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The H. K. Cushing Laboratory of Experimental Medicine

EDITED BY

G. N. STEWART, M. D., DIRECTOR

Volume IV

1915-1916

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THE INFLUENCE UPON TADPOLES OF FEEDING DESICCATED THYROID GLAND IN VARIABLE AMOUNTS AND OF VARIABLE IODINE CONTENTS.

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(From the H. K. Cushing Laboratory of Experimental Medicine of Western Reserve University, Cleveland.)

PLATE 78.

(Received for publication, July 2, 1915.)

In 1912 and 1914 Gudernatsch[1] reported his studies of the variable effects upon the growth and differentiation of tadpoles produced by feeding different kinds of animal tissues, such as thyroid, thymus, muscle, pancreas, liver, testicle, etc. His most striking findings were that thyroid feeding hastened the differentiation of the tadpoles, at the same time inhibiting their growth, so that he was able to obtain pigmy frogs; and that thymus feeding prevented or delayed their differentiation but favored their growth, so that giant tadpoles resulted. He used fresh tissues, and, in the case of the thyroid, without determining the amount of iodine present.

In view of the known relations of iodine to thyroid activity, it seemed probable that the iodine content of the thyroid fed might also modify its effect on tadpoles. With this in view a supply of tadpoles was brought to the Laboratory on May 9, 1914. These tadpoles were of uniform size, and their age was estimated at about one week.

The stock tadpoles were kept in large granite baking dishes. Those used for experimental observations were kept in small granite basins of about 200 cc. capacity, in which were placed a few small stones. The water in all the basins was completely changed twice

[1] Gudernatsch, J. F., Feeding Experiments on Tadpoles. I. The Influence of Specific Organs Given as Food on Growth and Differentiation, *Arch. f. Entwcklngsmechn. d. Organ.*, 1912–13, xxxv, 457; Feeding Experiments on Tadpoles. II. A Further Contribution to the Knowledge of Organs with Internal Secretion, *Am. Jour. Anat.*, 1913–14, xv, 431.

daily. The experimental basins were kept on tables in the middle of a large room, so that all would be exposed to similar light and temperature conditions. The room temperature was recorded every afternoon. After a few changes by way of trial, it was decided to feed the stock with fresh hog's liver every day, while the experimental animals were fed liver and thyroid on alternate days. The liver was cut up into small pieces, but not crushed. In the earlier experiments the liver was put into the basins in the forenoon and left till late in the afternoon, but this was abandoned because on hot days there was evidence of fermentation or putrefaction which led to the death of some of the tadpoles. The plan of allowing the liver to remain in the basins for one hour and then changing the water eliminated this danger even in the hottest weather. The thyroid was fed in the form of dried powder, in each case the iodine content having been previously determined by Dr. Marine. In the earlier experiments ten tadpoles were placed in each dish, with about 200 cc. of city tap water. Later but five tadpoles were placed in this quantity of water. Beyond taking photographs of the several series, no objective measurements were made of the changes produced.

The questions particularly studied may be summarized as follows: First, the effect upon both growth and differentiation of non-thyroid iodine; *e. g.*, potassium iodide and iodalbin (Parke, Davis & Co.). Second, the effect of thyroid feeding; (a) feeding constant amounts of a series of desiccated thyroids containing progressively increasing percentages of iodine; (b) feeding different quantities of one particular thyroid; (c) feeding thyroid obtained from different species of animals. Third, an attempt to counteract the effect of the thyroid feeding by keeping the tadpoles exposed to cold, by the use of cracker dust, quinine, egg white, egg yolk (both cooked and uncooked), and egg yolk extracted with acetone.

It may at once be stated that the effect of the potassium iodide solutions was negative. As to iodalbin, the results were indefinite. The animals showed early tail absorption, and most of them showed some emaciation at the time of their death; but they all developed some disease resembling a general body edema. Iodalbin contains about 21 per cent of iodine so loosely bound that the toxic effects from free iodine had to be considered, and hence these results can-

not be accepted as suggesting a thyroid-like action for iodalbin. Since these observations were made Morse[2] has published positive results from artificially iodized proteins, and states that the effect is comparable to that produced by thyroid iodine. Further observations must be made before this can be accepted, since there is no conclusive evidence that artificially iodized proteins exhibit an iodothyreoglobulin-like action.

The effect of thyroid feeding was very marked and closely associated with both the iodine content and the amount fed. The details will be exhibited later.

As to factors protecting against the effect of thyroid feeding, only two were found which were certain in their action; namely, exposure to cold and feeding carbohydrate in the form of cracker dust.

We may now examine more in detail the positive results.

The Effect of Thyroid Feeding.

Preparations of desiccated thyroid from human, canine, sheep, and ox glands were used. The human thyroids were obtained from Dr. Crile's clinic and include simple and exophthalmic goitres. All acted alike qualitatively. The sheep and ox glands available were too few to furnish an extended series of experiments, and may be dismissed from present consideration with the statement that there is no reason to believe that, with the material available, one could not get as gradated a series of results as we shall show can be gotten by the use of desiccated dog thyroid. With human glands a gradated series of effects was obtained, but it was not so sharp as with dog's thyroid. This is to be expected because of so many unknown factors in the life history, treatment, etc. Then, too, some of the thyroids had been in 10 per cent formalin for a day or two before desiccation. As regards the effect of formalin one can only state that it does not destroy the thyroid effect.

As examples of the experimental findings, the following protocols are exhibited.

Series I, Dog Thyroid.—Dishes 1, 2, and 3. The tadpoles in this experiment received 50 mg. respectively of three thyroids whose iodine contents were 0.05,

[2] Morse, M., The Effective Principle in Thyroid Accelerating Involutions in Frog Larvae, *Jour. Biol. Chem.*, 1914, xix, 421.

1.40, and 2.92 mg. of iodine per gm. of dried thyroid. This dosage was given every other day, as in all other experiments, unless otherwise indicated. The feeding was started May 16. No liver was fed in this case after the thyroid was started. The tadpoles in Dish 3 were all dead as early as 15 days, and in Dish 2 in 11 days. These were instances of high iodine contents. Four of the tadpoles in Dish 1, receiving thyroid of low iodine content, were living and active as late as Aug. 3—79 days—when the experiment was terminated. These tadpoles were about the size of the controls, but more differentiated, presenting formed (jointed) hind legs. Those in Dishes 2 and 3 died early, were much emaciated, and only slightly differentiated as compared with the controls.

Series I, Dog Thyroid.—Dishes 4, 5, and 6. This experiment is the exact duplicate of the previous one, except that liver was fed on alternate days. The tadpoles in Dish 6 were all dead in 10 days, and in Dish 5 in 2 days,—instances again of early death after feeding with thyroid of high iodine content. Those in Dish 4, getting low iodine thyroid, showed one tadpole still alive and active after 79 days. The tadpoles in this dish developed functional hind legs, were of large size, and had long, well preserved tails. Compared with the controls they showed no emaciation, but marked differentiation. They were larger than those in Dish 1, perhaps due to the liver feeding. In contrast, the tadpoles in Dishes 5 and 6, getting high iodine thyroid, died early, with much emaciation and before there was time for much differentiation. The emaciation was extreme. They literally melted down, the tails rapidly disappearing.

Series I, Dog Thyroid.—Dishes 7, 8, and 9. Here conditions were the same as in the first and second experiments above, except that the thyroid was given only twice. The tadpoles in Dishes 8 and 9, receiving high iodine thyroid, were all dead in 16 and 10 days, respectively, while those in Dish 7, getting low iodine thyroid, were not all dead till 57 days had passed. Those in Dishes 8 and 9 were the more emaciated. Differentiation was not especially affected in any. This experiment shows that only two doses of thyroid of a certain iodine strength will initiate emaciation and lead to early death, the effect being more marked in the case of thyroids with higher iodine contents. Gudernatsch also observed that one feeding with thyroid was sufficient to induce the emaciation and death.

Series II, Dog Thyroid.—In this experiment a series of thyroids containing respectively 0.05, 0.08, 0.18, 0.54, 0.71, and 1.40 mg. (Figs. 1 to 6) of iodine were fed in 50 mg. doses every other day, beginning May 23. Liver was given on alternate days. As early as four days the series as a whole showed a progressive decrease in size and activity in proportion as the iodine percentage increased. Within five days a most remarkable difference was seen, from large active tadpoles in Dish 1, getting the thyroid of lowest iodine content, to markedly emaciated, inert, and highly metamorphosed tadpoles in the dish getting the highest iodine thyroid. At the end of 72 days there was one tadpole living in each of the first three dishes. All were dead in Dishes 4 and 5 within 19 days, and in Dish 6 all were dead within 11 days. The number of days that intervened before the first tadpole died in each dish of the series ran as follows: 8 (accidental), 52, 33, 17, 9, and 5 days. For the second dead in each dish the figures ran: 54, 54, 35, 19, 11, and 7 days. For the third dead: 59, 68, 41, 15, and 11 days. This clearly shows that the death rate parallels the iodine contents. As to differentia-

tion the notes cannot be given in detail, but by way of summary it may be stated that the tadpoles getting high iodine thyroid (Dishes 4, 5, and 6) emaciated so rapidly and died so soon that little differentiation took place. In 41 days the tadpoles in Dish 1 had formed hind legs and were larger than the controls; *i. e.*, they showed marked differentiation together with growth instead of emaciation. On the same date the tadpoles in Dish 2 showed formed hind legs, but were smaller than those in Dish 1, while those in Dish 3 compared in every way with the controls. The final result then seems to be a balance between the tendency to emaciation and to hastened differentiation, and all degrees of differentiation may be associated with all degrees of size. Gudernatsch's more uniform results were undoubtedly due to using thyroid of more constant or high iodine content.

As previously stated, experiments were also made in which the quantity of a particular thyroid fed was varied; *e. g.*, feeding in 10, 20, 30, 40, and 50 mg. doses of some one particular thyroid. The first experiment of this kind to be reported is Series IV, where a dog thyroid containing 1.40 mg. of iodine per gm. of dried gland was fed beginning June 1. The number of days when all were dead ran, respective to the increasing amounts given, 20, 10, 8, 7, 8. Emaciation was very rapid and marked in all, so much so that in the larger doses there was little time for any differentiation. The tadpoles in Dish 1, on the other hand, getting only 10 mg. of thyroid, proceeded within 14 days to the formation of front and hind legs, large frog mouth, and prominent eyes.

Series VII, Dog Thyroid.—Here as in the previous experiment increasing doses were given of a thyroid containing only 0.54 mg. of iodine. Here the number of days within which all were dead were 32, 37, 37, 39, and 42, not very strikingly different. Emaciation was of little consequence in this series, and death was probably largely due to advanced differentiation. which was hastened in all as compared with the controls.

On the whole, the experiments of varying the quantity of thyroid fed are not nearly as clear cut as those where the iodine percentage was varied. I feel, however, that it is only a matter of obtaining a thyroid of suitable iodine content and arranging the quantities fed in a suitably gradated series, in order to get a well gradated series of effects.

The Protective Effect of Feeding Cracker Dust.

Series VIII, Human Thyroid.—In conjunction with some experiments on the possible inhibiting effect of quinine on metabolism, the following experiment was made. One group was fed cracker dust in addition to the regular liver feeding, and the other liver alone. Both groups received 50 mg. of human thyroid with an iodine content of 2.58 mg. per gm. of dried gland, every second day, beginning June 16. Dates of death were of little importance in this case, as they were mostly due to drowning on account of the high degree of differentiation reached. The tadpoles receiving cracker dust became large and acquired functioning hind legs, front legs, and frog-shaped bodies. Those receiving no cracker dust were smaller, had formed hind legs, but no front legs; on the whole they were more nearly like tadpoles, the first more like frogs. Both sets were larger than the controls.

Series XI and XII received every other day dog thyroid with an iodine con-

tent of 1.40 mg. Each series was divided into 5 dishes getting 10, 20, 30, 40, and 50 mg. of thyroid, respectively, beginning June 30. Series XI got cracker dust every second day alternately to the thyroid feeding. Within 8 days the cracker series showed a very distinct progressively increasing emaciation, proportional to the increasing amounts of thyroid fed. This bears out the previous experiments on the effect of variable quantity of thyroid. As early as the sixth day the other group, not getting cracker, showed a marked absorption of tails with decreased activity, while on the seventh day the disparity between the two groups was exceedingly well marked. All the non-cracker group were like small round balls with short conical tails. Owing to the severity of the reaction there was not much difference between the different members of this group. The death dates show a marked shortening of life in the group not receiving cracker. We may conclude then that the feeding of cracker dust delays the tendency of thyroid, when sufficiently active, to hasten death and also tends to prevent emaciation.

The Protective Effect of Exposure to Cold.

Believing that the effects thus far observed were largely due to the well known pharmacological action of thyroid of increasing metabolism, it was thought this action might be lessened by exposing the tadpoles to a lower temperature. Being cold-blooded animals, this would tend to lower their metabolism. With this in mind the following experiments were made.

Series V, Dog Thyroid.—To ten tadpoles kept in a refrigerator were given every second day 50 mg. of a thyroid (dog) containing 1.40 mg. of iodine, which had by previous experiments been shown to have a marked effect. The first dose was given on June 1. All the tadpoles were dead in 27 days, while of the controls kept at room temperature all were dead in 9 days. The controls became markedly emaciated. Those on ice became emaciated toward the end; but earlier, while the controls were still living, they were distinctly larger and less emaciated than the controls. Gradually their tails became absorbed, their bodies smaller, hind and front legs developed along with a frog facies, so that shortly before death they were small but well differentiated; *i. e.*, really pigmy frogs. The controls emaciated so rapidly that there was little differentiation.

Series VIII, Human Thyroid.—These tadpoles were fed cracker dust every second day in addition to the regular liver feeding, and were given every second day 50 mg. of a thyroid containing 2.58 mg. of iodine. Thyroid was started on June 16. One dish was kept on ice, one at room temperature. Of those on ice four were still living at the end of 49 days, when the experiment was terminated, while all of those kept at room temperature were dead in 28 days. Those on ice were of good size, with well preserved tails and slight hind leg buds at the last date of observation, Aug. 3. Those kept at room temperature, compared on the same dates with those on ice, were always larger. Also their differentiation went much further, in that they developed functioning hind legs, front legs, and frog-shaped body and head. And while they died earlier, death was not due to emaciation but to drowning, owing to their complete differentiation.

We may interpret this experiment as follows: At room temperature the stimulation of metabolism by this particular thyroid was not sufficient, in the presence of a more sufficient food supply (cracker), to lead to emaciation, but on the contrary the animals grew large and practically completely differentiated, meeting death by drowning. In the tadpoles kept on ice, metabolism was lowered by the cold so that the tadpoles grew only a little and differentiated only slightly; that is, the stimulating effect of thyroid on metabolism was to some extent counteracted. In the first experiment (Series V) cold protected against the extreme emaciation produced by a certain thyroid at room temperature. In the second experiment (Series VIII) cold tended to counteract the mild stimulation of a certain thyroid which at room temperature led to a high degree of differentiation.

DISCUSSION AND CONCLUSIONS.

We may conclude that the feeding of dried thyroid gland to tadpoles causes an early differentiation in proportion to the quantity fed or the percentage of iodine content of the gland used. With the larger doses and the higher iodine percentages, metabolism is stimulated to such an extent that the animals emaciate rapidly and die early, before there is time for much differentiation. With smaller amounts and lower iodine percentages the size of the animals is roughly inversely proportional to the amount or percentage, so that a close association of differentiation with pigmy size is not characteristic of thyroid feeding as such, as Gudernatsch seems to conclude. One may see early and marked differentiation along with large size. It all seems a question of dosage. The larger sizes are associated with slower differentiation, the smaller sizes with more rapid differentiation, and the smallest sizes may show no differentiation at all, due to the extremely rapid and marked emaciation, and early death. Non-thyroid iodine does not have this effect. The thyroid effect is inhibited by exposure to cold and by cracker feeding. Exposure to cold probably acts by lowering metabolism; cracker feeding, by substituting food other than the animal's own tissues to meet the increased demands caused by the stimulating effect of the thyroid feeding.

Gudernatsch in his earlier paper speaks of the thyroid as stimulating metabolism, which leads to early differentiation and suppresses growth. Later he seems to lean to the view that the thyroid possesses some specific influence on differentiation. It may all be a matter of words, but our present conception is that we are

simply dealing with the well known action of thyroid on metabolism. As the iodine content increases, the thyroid increasingly stimulates the metabolism of the tadpole, which undergoes changes in size, increased growth or rapid emaciation, according to the strength of the action. The tadpole being a larval form, the tissues first to be stimulated to increased metabolism, and later the first to be consumed, are naturally those tissues whose normal function is approaching a normal end, and which, in the normal course of events, are about to undergo metamorphosis. Hastening of differentiation seems then to ensue not as a specific stimulation of differentiation, but only to be the normal result of the stimulation of general metabolism. The seeming specificity of the result lies not in a new action of thyroid, but in its application to a living organism at a specific time in its development.

Most important, of course, is the confirmation of what we may be justified in regarding as an established fact; namely, that the activity and potency of the physiologically active substance of the thyroid is measurable in terms of its percentage iodine content.

Finally, it may be pointed out that the reaction of tadpoles to thyroid feeding is so sensitive that the procedure might well serve as a biological test for the activity of thyroid tissue, superior even to chemical methods.

EXPLANATION OF PLATE 78.

FIGS. 1 TO 6. Photographs of Series II, dog thyroid experiments. Experiment begun May 23 and photographed 7 days later. All were fed 50 mg. of thyroid every other day.

No.	1	received	thyroid	containing	0.05	mg.	of	iodine	per	gm.	dried.
"	2	"	"	"	0.08	"	"	"	"	"	"
"	3	"	"	"	0.18	"	"	"	"	"	"
"	4	"	"	"	0.54	"	"	"	"	"	"
"	5	"	"	"	0.71	"	"	"	"	"	"
"	6	"	"	"	1.40	"	"	"	"	"	"

No change is seen in Nos. 1, 2, and 3 because of the short time interval and the low iodine content of thyroid used, while Nos. 4, 5, and 6 show the characteristic increasing effect of thyroid paralleling the iodine content.

Fig. 1.

Fig. 2.

Fig. 3.

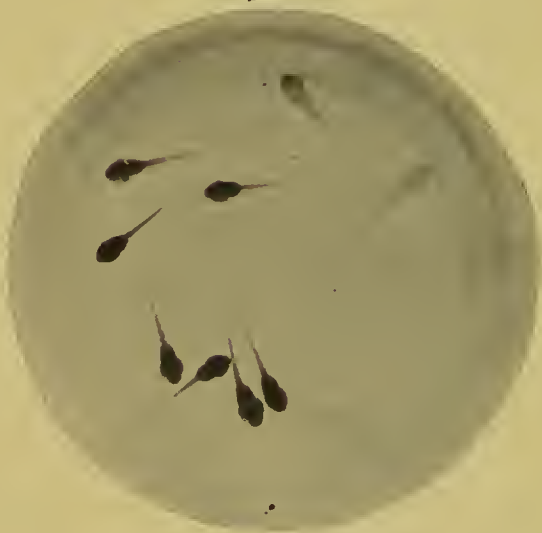

Fig. 4.

Fig. 5.

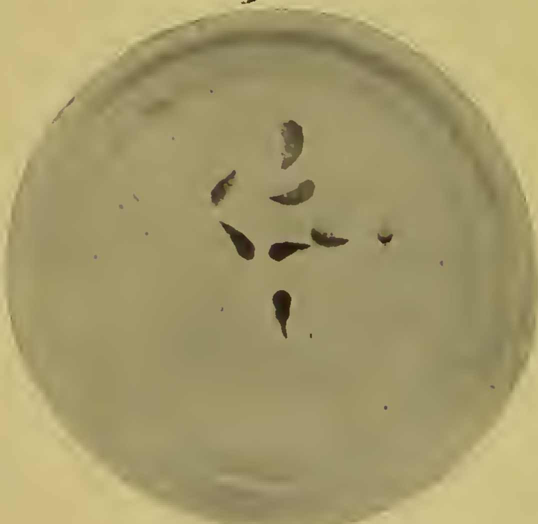

Fig. 6.

(Lenhart: Influence of Desiccated Thyroid Gland upon Tadpoles.)

The Coagulation Test for Syphilis, as Devised by Hirschfeld and Klinger

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THE COAGULATION TEST FOR SYPHILIS, AS DEVISED BY HIRSCHFELD AND KLINGER*

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Since the first appearance of the Wassermann test for syphilis, many short cuts and modifications have been devised or suggested and, we regret to say, most of them have failed to stand the test of time as well as the original. Moreover, several entirely new methods of diagnosis have been devised, of which Noguchi's cutaneous test has probably come the closest to being satisfactory, and that only in certain stages of the disease. In 1914, Hirschfeld and Klinger reported to the Congress of Internal Medicine at Wiesbaden that they had succeeded, by means of the process of coagulation, in distinguishing a syphilitic from a nonsyphilitic serum. At that time they had examined about 250 serums; they later reported that about 500 had been tested by a collaborator, and since then, in a personal communication, have written that around 1,000 successful tests have been made. During the past nine months, we have also been working with the technic, and have now done about 600 tests which we wish to report.

The reaction is based on the phenomena of coagulation of the blood. Hirschfeld and Klinger conceived the idea that there might be possibly a deviation of the cytozyme, akin to the deviation of the complement in the Wassermann reaction. To understand the details, it will be necessary to recall several of the principles of coagulation of the blood; and as Hirschfeld and Klinger have worked entirely on the schema as given by Bordet and Delange, we will only mention the work of these authors—it being outside the scope of this paper to discuss coagulation of the blood in its entirety. According to this schema, as we can see, coagulation is due to the precipitation of the fibrinogen of the plasma by the thrombin.

Calcium ion

Serozyme or prothrombin Cytozyme or thromboplastic substance

Thrombin Fibrinogen

Fibrin (coagulation)

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The thrombin itself is the product of three factors: first serozyme; an albuminoid thermostabile substance contained in the plasma; second cytozyme, a thermostabile substance, lipoid in nature, derived from tissues of the body, blood cells, platelets, etc., and very similar to lecithin and cephalin; third, calcium in the state of ionization (the non-ionized salts, for example, citrate, Arthus, Sabbatini and others have shown to be not active). The thrombin forms itself only in the presence of calcium, only a few seconds of time being required, and, once formed, it provokes coagulation of the fibrinogen, even in the absence of the ionized calcium salts. Bordet and Delange have shown that 1/1,000 or 1/20,000 mg. of the dried alcoholic extract of muscle or platelets forms thrombin capable of coagulating 0.5 c.c. of oxalate plasma.

Bordet and Delange entirely separate the two phases of coagulation. The first phase consists in the formation of thrombin by the interaction of serozyme and cytozyme in an ionized calcium medium. The solution of sodium oxalate precipitates the calcium salt in the plasma and thus causes the decalcification of the mediums. The coagulation is produced by the action of the thrombin formed in the first phase on the plasma (fibrinogen) added at the same time as the sodium oxalate solution (second phase). The separation of the two phases allows one to measure the quantity of thrombin formed in a given unit of time. The more thrombin there is in the solution, the quicker is the coagulation. Another advantage of their method consists in the employment of relatively pure solution. They take the blood in a paraffined tube containing a solution of sodium oxalate. The blood remains liquid, and after prolonged and speedy centrifugalization furnishes a plasma that is almost free from cytozyme. By recalcification the plasma is coagulated, and after the clot is expressed one obtains a serum rich in serozyme containing only traces of cytozyme. For cytozyme, Bordet and Delange use an extract of platelets or of organs, pure and sufficiently concentrated. To determine the strength of a substance in cytozyme, one proceeds in the following manner: The solution is treated with serozyme in calcified solution for fifteen minutes. Then the oxalate plasma is added. The time which elapses between the addition of the plasma and the beginning of the coagulation is inversely proportional to the amount of thrombin formed. If the plasma remains liquid, one concludes that the medium contains no thrombin.

Hirschfeld and Klinger have noticed the affinity of the cytozyme for the globulin of serum. The important rôle played by the globulins in most serologic reactions is a familiar fact. These findings have led them to inquire whether the technic of coagulation would not allow

them to discover certain phenomena of immunity. They have accordingly directed their attention especially toward a possible deviation of the cytozyme analogous to the deviation of the complement in the Wassermann reaction.

THE COAGULATION TEST

This reaction is based on the fact that the organ extracts employed in the Wassermann reaction represent very active cytozyme. This property of the cytozyme disappears after contact with a syphilitic serum, while it remains intact after a similar treatment with a normal serum.

In short, one measures the activity of a certain quantity of an extract after mixing it with a serum to be examined. If coagulation is not retarded sensibly and the extract is active in its coagulating power, the serum is normal. If, on the other hand, the coagulation is feeble or completely inhibited, the serum is syphilitic.

DIRECTIONS FOR THE REACTION

1. For serozyme, Bordet and Delange employed the serum of rabbit. Hirschfeld and Klinger have found that sheep's or goat's blood is richer in serozyme than that of the rabbit. These animals have less delicate platelets. They consider that paraffined tubes for receiving blood are not essential, if these vessels are perfectly clean and dry, warmed to 40 C. and the blood is drawn by a cannula. The latter authors have found beef blood unsuitable and we have likewise. We prefer paraffined vessels.

PREPARATION OF SEROZYNE

A 300-c.c. flask is filled with 100 c.c. of water and marked accurately at the fluid level. The flask is sterilized with dry heat to 180 C. for half an hour and then coated all over with paraffin. One puts into the flask 10 c.c. of the 1 per cent. sodium oxalate solution and 0.5 c.c. of 10 per cent. sodium chlorid solution for each 100 c.c. of blood. Mix them well by shaking. Fill with blood to the desired mark and shake it gently but thoroughly. Pour the blood thus prepared into centrifuge tubes heated to 40 C., and speedily centrifugalize it till the cellular elements have settled to the lower half of the tube. Remove the clear plasma with a pipet, taking care not to remove the red cells at the same time. Centrifugalize the clear plasma for a second time for at least thirty minutes to further get rid of the cytozyme present. Plasma thus obtained can be stored for three days in a refrigerator. It should be clear, yellowish in color and free from hemoglobin. This is the oxalate plasma.

FOR SEROZYME OR EXTRACT OF SERUM

To 10 c.c. of the oxalate plasma thus obtained, add 1.2 c.c. of the 1 per cent. calcium chlorid solution. Place the mixture in incubator until the clot is firmly formed. Express the clot by means of a pair of broad sterilized forceps. Sometimes it is necessary to repeat the procedure if not entirely clear. Then leave the clear liquid in the incubator for another half hour to destroy the further formation of thrombin. It is well to prepare the serozyme four or five hours before the experiment. Before use, the serozyme thus obtained should be diluted to five times its volume with 0.85 per cent. sodium chlorid, and the mixture should stand for one hour.

2. Calcified saline is prepared by mixing 100 c.c. of 0.85 per cent. of sodium chlorid and 5 c.c. of 1 per cent. solution of calcium chlorid. Fränkel and Thiele recommended 5 per cent. calcium chlorid in physiologic salt solution. We have tried their suggestion and find it does not work. Moreover, it is physiologically impossible, for it is a well-known fact that in strengths above 0.5 per cent. calcium solution clotting is impossible.

3. Oxalate plasma is prepared in the proportions given in Table 1.

TABLE 1.—Preparation of Oxalate Plasma

Oxalate plasma	20 parts
Solution sodium oxalate, 1 per cent.	20 parts
Normal saline	60 parts

This mixture should be prepared just before use.

4. For the organ extract, all alcoholic extracts may be used. Merck's preparation of guinea-pig's heart extract, of which 0.1 c.c. of a dilution of 1 : 160 causes coagulation after contact with serozyme in three to four minutes, is recommended by Hirschfeld and Klinger. We have prepared even better extracts of our own, both from guinea-pig and from human hearts.

TITRATION OF EXTRACTS

In order to ascertain what doses should be used in the experiment, there is prepared a series of dilutions of extract in 0.85 per cent. sodium chlorid solution, doubling each time the quantity of sodium chlorid solution. We recommend the initial dilution of 1 : 10 strength, to be followed consecutively by 1 : 20, 1 : 40, 1 : 80, 1 : 160 and 1 : 240. Mix 0.1 c.c. of each dilution with 1 c.c. of calcified saline and 0.5 c.c. of serozyme diluted one hour before. Let the mixture stand at room temperature for fifteen minutes, and add to it the mixture of oxalate plasma. One selects for the reaction the three consecutive dilutions, of which the first and second coagulate the plasma in from one to two minutes, and the third in from three to four minutes.

PREPARATION OF PATIENT'S SERUMS

In taking patient's blood, great care should be exercised to avoid hemolysis in the specimens to be tested. All serums should be inactivated at 58 C. for one hour in order to destroy the cytozyme present in them.

TECHNIC OF THE TEST

It is necessary to state that in order to make the test of diagnostic value, every detail is to be carried out accurately. We refer to the collecting of blood from the animals for experiments. The measurement must be carefully made in the quantity of blood taken and in the reagents used. The time for incubation of serozyme must be exact, and after the process it must be perfectly free from thrombin. Many a time, disappointment invariably follows only a slight overlooking of these seemingly little things. In every reaction, a preliminary titration of extract and control must be carried out before the main reaction is begun. It will be of great help if a preliminary test of one known positive and one known negative is also made. If the titration of extract fails to give a good result — either too rapid or too slow in the coagulation time — correct the fault at once before proceeding to the test proper.

TABLE 2.—Schema of Reaction

Patient's serum, 0.1 c.c.; heart antigen, 0.1 c.c.
Stand for one hour.
Calcified NaCl, 1.0 c.c.
Serozyme diluted, 0.5 c.c.

Stand for fifteen minutes.

Diluted oxalate plasma, 1.0 c.c.

After the addition of oxalate plasma, observe and record the time of coagulation. With a little practice, a large number of these specimens can be read at one time without difficulty.

THE CONTROLS

In order to make sure that the test is properly carried out, a series of controls must be made as follows:

The serozyme control consists of a mixture of diluted serozyme (1:5), 0.5 c.c., and calcified saline, 1 c.c. It should remain perfectly clear and liquid for hours, and show no signs of thrombin formation. This test should precede all others in the reaction.

The serum control (D) is to be carried out at the same time as the test proper with each patient's serum. It contains all the reagents except the extract, and it should remain liquid for at least three hours; it should not coagulate before the reading of all the specimens is completed.

TABLE 3.—Reaction as Used by Hirschfeld and Klinger and in Our Laboratory, Showing a Set of Experiments

	Patient	1:40 Minutes	Dilution of Extract 1:80 Minutes	1:160 Minutes	Serum Without Extract	Result of Test	Wassermann Result
1	Surgical	5	8	10	0	—	—
2	Surgical	5	8	10	0	—	—
3	Latent syphilis	8	0	0	0	+ +	+ +
4	Interstitial keratitis	9	0	0	0	+ +	+ +
5	Lesion on penis, ulcer mollis	5	8	10	0	—	—
6	Latent syphilis	8	0	0	0	+ +	±
7	Cerebrospinal syphilis (spinal fluid)	8	18 †	40 †	0	+	—
8	Gastritis	6	8	10	0	—	—
9	Asthma	5	8	11	0	—	—
10	Secondary anemia	5	8	10	0	—	—
11	Influenza	5	8	10	0	—	—
12	Latent syphilis (spinal fluid)	8	15	0	0	+ +	+ +
13	Cerebrospinal syphilis (spinal fluid)	10	0	0	0	+ +	+ +
14	Cerebrospinal syphilis (spinal fluid)	10	0	0	0	+ +	+ +
15	Known positive	7	0	0	0	+ +	+ +
16	Known negative ‡	4	6	8	0	—	—

* The figures indicate the time necessary for coagulation; 0 = no coagulation after four hours. The extract controls alone coagulated in one, two and three minutes, respectively.

† Feeble.

‡ Serozyme alone, 0.

The plasma control is to be carried out separately and before the main test is begun. It consists of a mixture of 1 c.c. of calcified saline, and 0.5 c.c. of serozyme diluted with 1 c.c. of diluted oxalate plasma. This mixture should remain in solution indefinitely.

Observe and record the time of coagulation.

After the adding of the oxalate plasma to all the tubes, the contents which are at first colorless and clear become flocculent and cloudy. The negative specimens starting from the first tubes gradually become thickened, gelatinous in consistency, and the coagulation takes place consecutively in from three to ten minutes in all the three tubes. The positive cases, however, remain either unclotted for hours in all the tubes or they very feebly and slowly coagulate. The time taken from reading is only of comparative value. There is no absolute standard of the coagulation time. It depends largely on the integrity of the serozyme, the strength of the cytozyme and the condition of the oxalate plasma. One reads, therefore, perhaps from two to eight minutes in one reaction and from ten to twenty-five in another. After a little practice one can judge accurately whether the given specimen is positive or negative by the character of the contents of the tubes. It is to be stated here that serozyme loses much of its power of thrombin formation after twenty-four hours' standing. Whenever possible it should be prepared anew.

COMMENT ON THE TEST

It is difficult to offer an explanation of the reaction. It is not primarily an anticoagulability of the syphilitic serum, because it affects its action only after contact with the organ extract. According to Hirschfeld and Klinger, in their early researches on the globulin of serum, there is a colloidal transformation of serum—a sort of ultramicroscopic precipitation of globulins due to contact with alcoholic extracts. This alteration of globulins probably effects absorption and diminution of the activity of the extract. This phenomenon is also observed, although in a less noticeable manner, with the cytozyme contained normally in the serum. One notices this with some syphilitic serums very rich in cytozyme which coagulate more rapidly in the control tubes and which do not furnish a sure result in the coagulation reaction. In such cases, the coagulation takes place very rapidly (in from two to five minutes) in the control tubes (D), while tubes with increasing doses of extract show retardation more marked in those that contain larger doses of extract. On the contrary a nonsyphilitic serum, rich in cytozyme, shows a coagulation more rapid in tubes containing the extract; while the control is slower, although it finally coagulates.

Hirschfeld and Klinger have found this test superior to the Wassermann in many instances, especially in cases of treated syphilis. Moreover, they have produced positive reaction to the Wassermann test by treating normal serums with emulsions of agar or of microbes, and also by prolonged agitation of diluted normal serums, whereas the coagulation test remained negative.

Their results show that the coagulation test for syphilis is as characteristic as the Wassermann.

An aqueous extract (cytozyme), Hirschfeld and Klinger find, has no effect on syphilitic serums. It is evident that the special change which the lipoid extract undergoes with the syphilitic serum cannot be due to anticytozyme, but that the reaction of the syphilitic serum with the lipoid extract leads to absorption of its coagulating powers, as a result of which it (lipoid extract) is less useful as cytozyme, or is even changed in its physical and chemical character.

COMPARISON WITH THE WASSERMANN REACTION

Of the 548 cases tested by us, fifty-one specimens are spinal fluids from different individuals. The classification given in Table 4 shows the number of the different diseases examined.

TABLE 4.—Classification of Cases

Diseases	No.
Infectious diseases, including fevers, pneumonia, rheumatism, arthritis, tonsillitis, etc.	15
Congenital syphilis	5
Cerebrospinal syphilis	17
Primary syphilis	23
Secondary syphilis	32
Tertiary syphilis	68
Latent syphilis	84
Treated syphilis	73
General paresis, psychoses, etc.	5
Tabes dorsalis	6
Gummas	4
Skin diseases, including acne vulgaris, rosacea, etc.	37
Medical cases, including diabetes, anemia, diseases of the respiratory, circulatory and digestive systems, etc.	131
Surgical cases	48
Total	548

As all the tests have been run parallel with the Wassermann, comments will be made only on the cases giving different results—either positive with this test and negative with the Wassermann, or vice versa. We employ the original Wassermann technic, using four different antigens for each serum. We use alcoholic human heart antigens reenforced with cholesterin.

Of the 548 cases of blood and spinal fluid examined, fifty-eight cases, or 10.5 per cent., give positive results with the coagulation test and negative results with the Wassermann. The diseases comprising these fifty-eight cases are given in Table 5.

TABLE 5.—Cases in Which the Coagulation Test Gave Positive Results and the Wassermann Negative

Latent syphilis	19
Treated syphilis	15
Secondary syphilis (spinal fluids)	2
Tertiary syphilis	11
Primary syphilis	4
Cerebrospinal syphilis	3
General paresis	2
Tabes dorsalis	1
Hodgkin's disease	1
Total	58

It is evident from these figures that the coagulation test is more delicate than the Wassermann. In our series it detects 10.5 per cent. more cases of syphilis than the Wassermann. In the latent and treated cases of syphilis, in which the Wassermann has often given negative results, the coagulation test has been positive. The four cases of primary syphilis in this series, in which infection was definite, and the lesions were characteristic of primary syphilis and persistent under local treatment, all gave negative results with the Wassermann, while the coagulation test was positive. Likewise in many tertiary cases the coagulation test was positive, while the Wassermann reaction was negative. In general paresis, tabes dorsalis and the cerebrospinal syphilis quoted above, there was, in most cases, not even a trace of complement deviation with the Wassermann reaction, while they came out positive with the coagulation test. There is one case of Hodgkin's disease not accounted for. On account of the lack of history, we are not able to comment on it.

It must be pointed out here that there are a few cases on our record having positive reaction with the coagulation test and negative with the Wassermann, and we cannot find any justification for such results from the history given. Repetition of the test with fresh reagents is of course highly advisable in these cases. The following cases are on record, and we have since had one or two others. In this, however, the test is probably as fallible as the Wassermann.

J. P., Hodgkin's disease, coagulation ++, Wassermann ±.
A. S., acne vulgaris, coagulation ++, Wassermann —.
L. W., pityriasis rosea, coagulation ++, Wassermann —.

On the other hand, it has been observed from time to time that a few serums react negatively with the coagulation test and positively with the Wassermann. Of the 548 cases, we have three specimens giving persistently negative results with this test and positive with the Wassermann. For example, we have:

B. A., syphilis, coagulation —, Wassermann ++.

L. B., spinal fluid, syphilis, coagulation —, Wassermann ++.

P., spinal fluid, syphilis, generalized eruption, coagulation —, Wassermann ++.

In general, we have found that hemolyzed specimens tend to produce coagulation in all the tubes, regardless of the presence or not of tissue extract.

We have so far tested only fifty-one specimens of spinal fluids from different patients. The results have been most gratifying. In quite a few cases the Wassermann has given negative results while the coagulation test has been positive: in fact, of the fifty-one cases, the coagulation test gives eleven more positive than the Wassermann, making a difference of 21 per cent. more positives for the coagulation test. The original publication reports unfavorable results with the spinal fluids tested. Our small experience, we believe, allows us to state that the spinal fluid, inactivated at 58 C. (136.4 F.) for half an hour and used in dose of 0.4 c.c., gives good results with this test.

The question arises as to the effect of the age of the serums on this coagulation test. We have tested about 150 serums of different ages and at different times. The time elapsed has been from two weeks to two months in different series of the specimens. The results have been uniformly good. With the exception of specimens showing deterioration, they all stand well for at least four weeks, if kept on ice. When a serum deteriorates, it generally gives a positive reaction. It is safe, therefore, to make a conservative estimate that all serums which have been inactivated at 58 C. for one hour can be kept in an ice chest for one week or possibly more without the reaction being affected.

For the purpose of studying the stability of the antibodies in the serum, we have made the following experiments: We have heated a few specimens of serums to 65 C. (149 F.) for from three quarters of an hour to an hour without generally altering the reaction. A few specimens heated to 70 C. (158 F.) or over showed a tendency of the negative specimens to become positive.

While the results are encouraging with our work for the past nine months, we would still recommend that all the tests should be done hand in hand with the Wassermann. This is especially important with those who have had little or no experience in serologic work. In the hands of experienced workers, this is unquestionably a more delicate test than the Wassermann, and only further work can show us its scope and limitations.

CONCLUSIONS

1. The coagulation test carried out by thoroughly reliable and conscientious workers is quite as specific as, and more delicate than the Wassermann, in cases of treated, latent and cerebrospinal syphilis.

2. Syphilitic cases, after prolonged and effective treatment, give negative results with the coagulation test, as with the Wassermann.

3. A few primary cases have given a positive result with the coagulation test, while the Wassermann was still negative.

4. Spinal fluids, after inactivation for half an hour at 58 C., give good results with the coagulation test, if used in doses of 0.4 c.c.

Our deepest gratitude is due to Prof. G. N. Stewart for his valuable suggestions and advice in carrying out this work.

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Studies in thyroid transplantation.

I. Data Relative to the Problem of Secretory Nerves.

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During the past two years we have utilized the method of thyroid transplantation in rabbits in the attempt to get further data concerning certain questions in the physiology and pathology of this tissue. One of these questions is that of the necessity or not of specific secretory nerves to the gland. The observations of Anderson, Berkeley and Rhinehart have shown that in the thyroid both vessels and gland cells are abundantly supplied with nerve fibers. Stewart, Francois Frank and others have demonstrated the richness of the vasoconstrictor nerve supply, and Von Cyon demonstrated the presence of vasodilator fibers, both sets of fibers for the most part reaching the gland through the superior laryngeal nerves. More recently Asher and Flack and Ossokin have published physiological evidence which they think supports the view that the gland is under the control of secretory nerves, and Beebe and his associates have found that prolonged stimulation of the thyroid nerves causes a slight reduction in the iodin content which they interpret as indicating the presence of secretory nerves.

The method of transplantation eliminates many of the physiological and technical difficulties and objections of the acute experiments.

It has been found that under certain conditions thyroid tissue may be readily transplanted in widely separated parts of the body, as for example in the adrenal, ovary, subperitoneal tissues, muscle, subcutaneous fascia of the neck, chest and abdomen, and also, though with more difficulty, in the spleen and bone marrow. By transplanting and removing a sufficient amount of the main gland, care being taken to avoid all contact with iodin, we have always obtained compensatory hyperplasia of the remaining

stump, and in addition a simultaneous and similar degree of hyperplasia of any existing transplants independent of their location. Thus we have seen such reactions in ovarian, adrenal and subcutaneous transplants of the chest, neck and abdomen.

Now, if one gives very small doses of some idoin-containing substance, whether by mouth or by the use of a little tincture of iodin as in skin sterilization, involution promptly occurs in from two to three weeks which effects the transplants irrespective of their location in the same way as the main thyroid gland stump is effected. We have seen no exception to this except in cases where the total amount of thyroid tissue was below the level at which iodin will protect against thyroid hyperplasia. Also if iodin is administered prior to or at the time of transplantation, no hyperplasia of either the original gland or transplants occurs until the effect of the iodin has fallen to the level of inducing an insufficiency. Likewise if iodin is administered following transplantation, no hyperplasia ordinarily occurs during the time of such administration. We have followed such thyroid transplants for as long as 271 days.

If now a large part of the transplanted thyroid tissue and of the original gland, thus involuted, is removed, the remaining thyroid transplants and the remaining portion of the stump undergo active hyperplasia for the second time. This is similar in all essentials to the effects seen in dogs following alternate partial thyroid removals and iodin administrations. There is evidence also that transplanted thyroid tissues function. We have observed four rabbits showing marked amelioration of the symptoms of operative myxedema associated with active hyperplasia of subcutaneous abdominal transplants.

In view therefore of the facts that (1) under favorable conditions thyroid tissue may "take" and grow in widely different parts of the body; (2) that such transplanted tissue undergoes hyperplasia simultaneously and is histologically identical with that of the original gland stump; (3) that iodin induces an involution alike in both the transplanted and non-transplanted tissue, we believe (*a*) that the thyroid may function as a true blood-vascular gland in that the stimuli which cause these hyperplasias may reach the gland cells through the blood stream and that

influences causing thyroid involution may be transmitted by the same means; (*b*) that while these observations do not affect the question of the existence of specific secretory fibers, they demonstrate that such fibers are not essential in order that thyroid tissue may exhibit the characteristic morphological and physiological. changes known to be associated with great variations in functional activity; (*c*) that these data emphasize the necessity for additional evidence on the question of specific secretory fibers for the thyroid.

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STUDIES ON THE CIRCULATION IN MAN.

XII. A Study of Inequalities in the Blood Flow in the Two Hands (or Feet) Due to Mechanical Causes (Embolism, Compression of Vessels, Etc.) or to Functional (Vasomotor) Causes, with a Discussion of the Criteria by Which the Conditions Are Discriminated.

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In this paper a few typical cases are discussed to illustrate the criteria referred to in the title. Other cases presenting inequalities in the flow are included in Paper XIII of this series,[1] under unilateral peripheral neuritis and hemiplegia. Some have been published in previous papers, and of these one or two will be briefly alluded to. The flow observations are summarized in Table I.

A criterion which could be predicted *a priori* for a blood flow diminished by a mechanical obstruction would be the approximate constancy of the ratio of the flow in the obstructed part to that in the corresponding normal part in measurements made at such short intervals that collateral circulation could not be appreciably increased in the interval. If the obstruction is so great that the chief resistance of the vascular path is situated there, it is clear that a further criterion would be the lack of any marked response of the blood flow in the part to vasoconstrictor or vasodilator influences; *e. g.*, to reflex vasomotor effects from the contralateral part. It will, of course, depend upon the degree of the obstruction and the extent to which a collateral circulation has been opened up how great an effect on the flow will be produced through the vasomotors. Under no circumstances could we expect the ratio of the flow in the

[1] Stewart, G. N., *Arch. Int. Med.*, 1915, xvi (in press).

obstructed part to that in the normal part to be increased by conditions favoring vasodilatation acting equally on both parts or on the whole surface, for example, by an increase of the air temperature, whereas general cutaneous vasodilatation might very well alter the ratio to the disadvantage of the affected part. On the other hand, purely central changes, affecting only the driving power of the heart, would leave the ratio unchanged, however great the absolute changes in the flows might be.

These considerations have been verified in a number of cases. One of these has been already described.[2] The innominate and right common carotid arteries were ligated by my colleague, Dr. Carl Hamann, in a woman 68 years old, for subclavian aneurysm. About a month after the operation the ratio of the flow in the right hand to that in the left was 1 : 3.54 and 1 : 3.48 on two successive days. The stability of the ratio, although the flow in both hands was somewhat greater at the first than at the second examination, is obvious. Also practically no vasodilatation was caused in the right hand when the left was immersed in warm water. The stability of the ratio is clearly, and the failure of the contralateral reflex to influence the flow is almost certainly, associated with the still very effective mechanical block on the arterial path of the limb. Sixteen weeks later the collateral circulation had opened up so well that the ratio had increased to 1 : 1.3, and the vasomotor reflexes from the left to the right hand were now distinctly shown by the change in the blood flow.

A case with a different kind of mechanical block, namely, embolism (and thrombosis) in the left arm and the right leg, illustrates equally well the criterion of stability of the ratio of the flows. There was apparently at one time some temporary plugging of vessels in the right arm also, but this cleared up.

Costa B., a dyer, aged 47 years, was in Lakeside Hospital from Apr. 13, 1914, to May 9, 1914, suffering from rheumatic fever, and left with the physical signs of mitral stenosis and insufficiency. On July 31, 1914, he was readmitted to the hospital. That morning while at work he suddenly felt a severe pain in the right leg, worst in the groin. No pulsation could be detected in the right dorsalis pedis. The anterior tibial pulse could be felt, but was very feeble. No pulse in the right popliteal. Good pulsation in the left leg in all accessible arteries. No pulse in the left radial artery, but the right is strong, rhythmic, regular, and well sustained. The vessel wall is palpable, but not nodular. A strong pulse can be felt in the right brachial. Blood pressure, left arm, systolic 114, diastolic 85.

Sept. 26, 1914. The pulse is obliterated in the left radial. The left hand is cold and pains him. Sept. 30. He says there is tingling of the left hand and right foot. The left radial pulse is absent and never returned after this. The right radial pulse is diminished. Right brachial felt.

Oct. 3, 1914. He says that there is no discomfort except tingling in the right foot. Both extremities are warm. The right femoral pulse can be felt, but not the dorsalis pedis. No pulse in the left radial or brachial. Pulse in

[2] Stewart, *Arch. Int. Med.*, 1913, xii, 678.

right radial and brachial. On Oct. 5 it is stated that the right radial pulse could not be felt. On Oct. 8 the right radial pulse was again felt, and was always present thereafter. On Oct. 10 he complains of pain in the left shoulder and down the arm to the elbow. Physical signs of (compensated) mitral stenosis and insufficiency. The blood flow was examined on Oct. 26, 1914, at which time no improvement had occurred in the permeability of the vessels which could be detected by palpation. The left foot is warmer than the right to the touch.

First Examination of Blood Flow.—Costa B., Oct. 26, 1914. Hands in bath at 2.56 p.m., in calorimeters at 3.07, out of calorimeters at 3.28. As always, unless otherwise mentioned, the quantity of water in each hand calorimeter was 3,015 cc.

Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.	Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.
3.06½	31.63	31.53		3.18	31.72	31.435	
3.08	31.59	31.48		3.19	31.75	31.43	22.4
3.09	31.595	31.48	21.4	3.20	31.78	31.425	
3.10	31.61	31.475		3.21	31.80	31.42	
3.11	31.62	31.47	21.3	3.22	31.82	31.41	22.6
3.12	31.62	31.46		3.23	31.84	31.405	
3.13	31.63	31.46	21.4	3.25	31.895	31.40	
3.14	31.65	31.455		3.26	31.92	31.40	
3.15	31.67	31.45	21.7	3.27	31.945	31.395	
3.16	31.695	31.455		3.28	31.98	31.385	22.8
3.17	31.71	31.44	22.0	3.41	31.79	31.22	

Cooling of calorimeters in 13 minutes, right 0.19°, left 0.165°. Volume of right hand 473 cc., of left 441 cc. Water equivalent of calorimeters with contents, right 3,473, left 3,448. Pulse in carotid 102.

Feet in bath at 3.44½ p.m., in calorimeters at 3.55½, and out of calorimeters at 4.24. As always, unless otherwise mentioned, the quantity of water in each foot calorimeter was 2,775 cc.

Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.	Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.
3.55	32.17	32.19		4.14	31.69	31.95	22.0
3.57	32.03	32.06	21.9	4.16	31.68	31.97	
3.59	31.97	32.00		4.18	31.67	31.99	22.0
4.01	31.90	31.96	22.0	4.20	31.66	32.02	
4.03	31.85	31.93		4.22	31.65	32.04	22.05
4.05	31.78	31.91	22.0	4.24	31.64	32.06	
4.07	31.76	31.91		4.26	31.59	32.03	
4.09	31.73	31.91	22.0	4.34	31.40	31.84	22.1
4.12	31.70	31.93					

Cooling of foot calorimeters, 0.19° in 8 minutes for right and left. Volume of right foot 1,191 cc., of left 1,188 cc. Water equivalent of foot calorimeters with contents, right 3,856, left 3,854. Rectal temperature 37.45° C.

The blood flow in the hands for the last fifteen minutes in the calorimeters was 6.03 gm. per 100 cc. per minute for the right hand, and 1.28 gm. for the left, with room temperature 22° C. The ratio of the flow in the left foot to that in the right was 1 : 4.71. For the feet the flows were 1.25 gm. per 100 cc. per minute for the right, and 2.50 gm. for the left, with room temperature 22° C. calculated for the last 15 minutes in the calorimeters when the flows had become steady (ratio 1 : 2). The ratio of the sum of the foot flows to the sum of the hand flows was 1 : 1.04, and the ratio of the flow in the normal (left) foot to that in the normal (right) hand, 1 : 2.41, both within the normal range for the ratio of foot to hand flow.

The man was discharged on Nov. 20 from Lakeside Hospital, and was admitted at the City Hospital on Feb. 2, 1915. He complains of pain in the right leg from the groin down. When he walks a little, the pain gets worse. There are also shooting pains down the leg. On placing a constricting band on the left arm, the superficial veins filled slowly. When the band was put on the right leg, none of the superficial veins filled. The veins of the left leg and right arm filled rapidly (Feb. 16). On Feb. 9 the blood examination gave erythrocytes 5,100,000, leucocytes 6,400. Wassermann negative. Blood pressure (Feb. 9), systolic 95, diastolic 65; (Feb. 11) 110 and 75. On admission the boundaries of the cardiac dullness were the third rib, the right sternocostal margin, and 2 cm. to the left of the nipple line. The blood flow was examined on Feb. 24, 1915. At this time the grip of the left hand was strong, scarcely weaker than that of the right. The right foot and lower leg feel markedly cold to the touch, and there is no pulse in the dorsalis pedis or elsewhere in the leg. No pulse at the left wrist, and the left hand is colder to the touch than the right. There is no difference in the nails of the two hands. He complains of pains in the right leg and says that it feels tired all the time. The left hand does not now trouble him much. There is some wasting of the right leg.

Second Examination.—Feb. 24, 1915. Hands in bath at 3.12 p.m., in calorimeters at 3.22, and out of calorimeters at 3.35.

Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.	Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.
3.21	31.89	31.82		3.31	32.09	31.87	
3.23	31.85	31.80	23.8	3.32	32.12	31.88	23.8
3.24	31.88	31.82	23.8	3.33	32.16	31.89	
3.25	31.90	31.825		3.34	32.195	31.895	
3.26	31.93	31.83		3.35	32.26	31.90	23.9
3.27	31.97	31.84	23.8	3.55	32.06	31.67	
3.29	32.03	31.86	23.7				

Cooling of calorimeters in 20 minutes, right 0.20°, left 0.23°. Volume of right hand 498 cc., of left 452 cc. Water equivalent of calorimeters with con-

tents, right 3,493, left 3,457. Pulse 81. The right radial pulse was surprisingly difficult to feel considering the fair blood flow.

The blood flow for the right hand at this examination was 6.96 gm. per 100 cc. per minute, and for the left hand 2.54 gm. (for 11 minutes in the calorimeters), with room temperature 23.8°. For the right hand this is practically the same as on Oct. 26, 1914, four months earlier, considering the higher room temperature at the second examination. In the left hand, however, the flow is twice as great as on the first occasion, so that the ratio of the hand flows is now 1 : 2.74, indicating a great improvement in the collateral circulation in the left hand. This is quite in accordance with the general condition of the hands. There is, of course, still a decided mechanical obstruction on the left side, and the new ratio of the hand flows is stable for successive measurements made at short intervals, as shown by the third examination.

Third Examination.—Feb. 26, 1915. The pulse rate was considerably greater than at the last examination, and the superficial veins of the hands were distinctly better filled. The veins of the right hand were fuller than those of the left, and the resistance to compression of the veins by the finger was greater in the right hand. The pulse was felt in the right brachial although not strongly, and was not felt in the left brachial. Feet in bath at 2.11 p.m., in calorimeters at 2.25½, out of calorimeters at 2.49. Pulse 102, counted in the carotid, as it was difficult to count it at the right wrist, although regular.

Time.	Temperature of			Time.	Temperature of		
	Calorimeters.		Room.		Calorimeters.		Room.
	Right.	Left.			Right.	Left.	
2.24	31.92	31.77		2.39	31.855	32.74	23.7
2.27	31.91	31.86	23.4	2.41	31.86	32.87	23.3
2.29	31.89	31.995	23.4	2.43	31.85	32.99	23.1
2.31	31.88	32.14	23.2	2.45	31.845	33.12	23.1
2.33	31.87	32.30	23.5	2.47	31.84	33.24	23.4
2.35	31.865	32.47	24.1	2.49	31.79	33.27	
2.37	31.86	32.61	24.1	3.18	31.42	32.79	

Cooling of foot calorimeters in 31 minutes, right 0.37°, left 0.48°. Volume of right foot 1,132 cc., of left 1,199 cc. Water equivalent of foot calorimeters with contents, right 3,812, left 3,862.

Hands in bath at 3.13½ p.m., in calorimeters at 3.23½, and out of calorimeters at 3.36.

Time.	Temperature of			Time.	Temperature of		
	Calorimeters.		Room.		Calorimeters.		Room.
	Right.	Left.			Right.	Left.	
3.23	31.48	31.34	23.5	3.31	31.80	31.46	24.3
3.25	31.48	31.36	23.3	3.32	31.87	31.48	24.2
3.26	31.51	31.37	23.1	3.33	31.90	31.49	
3.27	31.58	31.385	23.4	3.34	31.95	31.505	24.3
3.28	31.62	31.40		3.35	32.00	31.52	24.2
3.29	31.70	31.42	24.1	3.36	32.12	31.53	
3.30	31.73	31.43	24.3	3.52	31.96	31.37	

Cooling of hand calorimeters, 0.16° for right and left in 16 minutes. Volume of right hand 407 cc., of left hand 457 cc. Water equivalent of calorimeters with contents, right 3,492, left 3,460. Rectal temperature 37.85°.

The blood flow in the right hand on Feb. 26 was 9.98 gm., and in the left hand 3.70 gm. per 100 cc. per minute for the last 10 minutes in the calorimeters, with average room temperature 24° C. The flow in both hands is considerably greater than two days previously, corresponding to the increased pulse rate, but the ratio is exactly the same (1 : 2.70). The flow in the right foot was only 0.70 gm. per 100 cc. per minute even with the increase in the general circulation, a considerably smaller flow than at the first examination, four months previously, while the flow in the left foot was 6.50 gm., with room temperature 23.5° C., a great increase. The ratio between the flows in the two feet was 1 : 9.28, which shows a decided decrease in the circulation in the right foot. This agrees completely with the other signs of deterioration, and suggests the probability of impending gangrene. The flow, actually measured in the right foot, is probably still sufficient to nourish the tissues, since considerably smaller flows have not infrequently been met with in other conditions without gangrene. But should a further examination show that the diminution in the flow is still progressing, that of itself would be sufficient to indicate a grave prognosis. It is an interesting fact that the ratio of the sum of the foot flows to the sum of the hand flows (1 : 1.00) is precisely the same as four months ago, in spite of the great changes in the ratios between the two hand flows and between the two foot flows, and in the absolute amount of both foot and hand flows. This suggests that the blocking of the vascular path to one leg (doubtless the diminution in the flow extends to the whole of the right posterior extremity) is associated with a reciprocal dilatation of the path to the other leg, so that the normal partition of the blood between the legs and the rest of the body is scarcely disturbed. That is to say, the blood which normally finds its way through the two common iliacs seems eventually, when the main part of the path from one common iliac is blocked, still to find its way through the one which remains pervious, the normal limb making room, it may be supposed by vasodilatation, for an additional quantity of blood.

It would, of course, be rash to generalize from one or two measurements of this kind, but the result in this case is so precise that it needs an explanation. If we reflect that one important function of the circulation, and relatively more important in the limbs than elsewhere on account of the greater proportion of their surface to their mass, is the elimination of heat, it will not appear fantastic to suggest that when the blood flow through the skin of one leg is greatly interfered with, it might be advantageous for the flow through the skin of the other leg to be accelerated. The same consideration applies to the muscles in so far as interchange between them and the other tissues is of general utility in the metabolism. The regulation of the blood pressure may also be facilitated by such a redistribution of the blood, which, if it occurs, may be assumed to be brought about, mainly at any rate, through the vasomotor system. An occlusion coming on gradually and never becoming complete presents, of course, different conditions from a complete occlusion caused by ligation of large arteries or by amputation. One important difference is that the tissues fed by

the partially occluded vessels continue to contribute to the total metabolism of the body and to the heat production, and must therefore to some extent influence the blood flow in the surfaces from which heat is lost and the organs concerned in excretion.

Note Added May 7, 1915.—Another examination of the blood flow in Costa B. was made on Apr. 7. The flow in the left hand was 3.43 gm. per 100 cc. per minute, and in the right hand 13.11 gm., with room temperature 24.5° C. (ratio 1 : 3.82). In the feet the flows were 1.51 gm. and 7.43 gm. for the right and left, respectively, with room temperature 23.3° C. (ratio 1 : 4.92). The ratio of the combined foot flows (per 100 cc. per minute) to the combined hand flows was 1 : 1.85; *i. e.*, practically the same as at the previous examinations. The man died on May 4. For 4 days before death the right leg and foot had been numb and discolored by subcutaneous hemorrhages. At the necropsy the right common iliac artery was found completely occluded by an old organized thrombus firmly adherent to the artery. A similar thrombus occupied the left subclavian artery. A fresh thrombus was found in the left external iliac artery. It was freely movable. There was marked mitral stenosis with hypertrophy of the left auricle, and the valve was covered with vegetations.

An apparent instance of a reciprocal relation of the lymph flow and blood flow in a part which leads to increased blood flow when the outflow of lymph is obstructed was observed in a case already reported.[3] The case was diagnosed as Hodgkin's disease. There was great and persistent edema in both legs and nowhere else in the body. The swelling remained quite unaltered during the five weeks of the man's stay in the hospital. It coincided with a relatively good blood flow in the feet, which was interpreted as indicating that the obstruction responsible for the edema was on the lymph path rather than on the venous path. The flow in the feet was particularly large in proportion to that in the hands (ratio of combined foot flows to combined hand flows 1 : 0.96). The sum of the foot flows per 100 cc. of part per minute actually exceeded slightly the sum of the hand flows, a very rare condition in our observations. It was suggested that far from being interfered with, the blood circulation in the edematous legs was accelerated through local vasodilatation.

It is known that the exchange between the blood in the capillaries and the tissues does not consist merely in the passage of materials out of the blood, but also in the passage of materials, including water, from the tissues into the blood. The intracellular liquids and tissue lymph are naturally in relation both with the blood and with the lymphatic lymph, and their normal composition is maintained by interchange with both. Is it not probable that when the lymphatic channels are blocked, and the elimination of waste products and the regulation of the quantity of tissue lymph by way of the lymphatics interfered with, the flow in the alternative channels, the blood capillaries, may be increased, so as to increase the excretion by way of the blood? The associated vasodilatation may very well be brought about by the accumulation of one or another of the waste products.

In the next case the question was raised at the clinical examination whether the circulatory changes observed in one hand could be at-

[3] Stewart, *Arch. Int. Med.*, 1913, xii, 678.

tributed to injury or irritation of the brachial plexus or some of its constituent cords. The blood flow measurements indicated clearly that the phenomena were due to mechanical obstruction on the arterial path of the limb, and further, a point of importance in connection with the question whether operative interference was advisable, that the blood flow in the affected hand was quite sufficient to nourish the part.

Walter L., aged 25 years, height 5 feet 10 inches, weight 210 pounds, a powerfully built man, well nourished, with a good deal of subcutaneous fat, was admitted to the City Hospital on Oct. 25, 1914, suffering from a gunshot wound. His partner who was shooting rats with a small rifle at the lunch hour accidentally shot him, the bullet (caliber No. 22) entering the right side of the chest close to the sternum and lodging near the right shoulder, as was afterwards shown by the x-ray. He drove home and then came at once to the hospital. The wound bled at first with a squirt, but soon stopped and has not bled much since. The other man was 5 feet 8 inches in height and the gun was pointed directly at the front of the patient and slightly upward. The general course of the bullet when it struck the patient was slightly upward, and very slightly to his right. On admission he complained of a continual dull ache localized under the armpit, and of pain when he breathed deeply. The fingers of the right hand are numb, but he can move them perfectly well. There is a tendency for the thumb and forefinger to flex themselves.

Nov. 1. He complains that the fingers of the right hand remain flexed rather than straight, and says that he must lay his hand upon something to keep the fingers from doubling up. It appears as if the median nerve were irritated. He can now move his right shoulder a little in all directions. There is a large hematoma in the axillary region, and the ecchymosis extends downwards to the waist line and also above the deltoid. On Nov. 4 he complains of severe pain in the deltoid region. On Nov. 5 the amplitude of the right radial pulse is less than that of the left. The pulse is regular. On Nov. 6 he still complains of his hand. The index and middle fingers now seem to be extended most of the time. On Nov. 11 there seems to be no pain in the arm, and the patient is allowed to be up. The index, middle finger, and, to a less extent, the thumb are numb. Tactile sensation and pain sensation are diminished on the palmar surface of these fingers and on the dorsal surface of their two last phalanges. The skin on the palmar surface over the median nerve distribution right up to the wrist is scaly, while the ulnar area of the palmar surface is normal. The finger nails on the right hand have grown less than on the left hand. The inner portion of the thenar eminence is atrophied. The grip between the little and ring fingers is less strong than in the left hand. The inequality in the radial pulses continues. The x-ray shows the bullet in the axilla about one inch below the lower lip of the glenoid.

The question was put by the surgeon in charge of the case, whether the diminished pulse could be attributed to injury of the

brachial plexus or to pressure on it, and, in particular, whether the blood flow in the affected hand was so much diminished as to threaten gangrene and therefore to call for surgical interference.

First Examination of Blood Flow.—Walter L. Nov. 13, 1914. Hands in bath at 2.10 p.m., in calorimeters at 2.20¾. At 2.38 left hand put into water at 8.2° C. At 2.50 left hand put into water at 44°. At 3.04 right hand out of calorimeter.

Time.	Temperature of Calorimeters. Right.	Left.	Room.	Time.	Temperature of Right calorimeter.	Room.	Time.	Temperature of Right calorimeter.	Room.	Notes.
2.20	31.06	31.04		2.39	31.44		2.57	31.725		
2.22	31.00	31.12		2.40	31.46	23.1	2.58	31.75		
2.23	31.02	31.18	23.3	2.41	31.47		2.59	31.775	23.3	
2.24	31.03	31.27	23.4	2.42	31.48	23.2	3.00	31.79		
2.25	31.05	31.35		2.43	31.49		3.01	31.82		
2.26	31.09	31.43	23.4	2.44	31.505	23.1	3.02	31.84	23.3	
2.27	31.12	31.52		2.45	31.52		3.03	31.89		
2.28	31.14	31.595		2.46	31.56	23.1	3.04	31.925	23.4	
2.29	31.16	31.67	23.4	2.47	31.595		3.19	31.715	23.3	Lt.
2.30	31.19	31.74		2.48	31.605	23.1				31.80
2.31	31.22	31.81		2.49	31.615					
2.32	31.25	31.90	23.3	2.50	31.63					
2.33	31.28	31.98		2.51	31.64	23.3				
2.34	31.31	32.06	23.3	2.52	31.65					
2.35	31.33	32.13		2.53	31.66					
2.36	31.36	32.20		2.54	31.68	23.3				
2.37	31.39	32.28	23.2	2.55	31.695					
2.38	31.42	32.345		2.56	31.71	23.3				

Cooling of calorimeters, right 0.21° in 15 minutes, left 0.545° in 41 minutes. Volume of right hand 503 cc., of left 464 cc. Water equivalent of calorimeters with contents, right 3,497, left 3,468. Rectal temperature 37.42° C.

For 15 minutes before the vasomotor reaction was tested the blood flows of the two hands came out 5.32 gm. per 100 cc. per minute for the right hand, and 14.76 gm. for the left hand, a ratio of 1 : 2.77, with room temperature 23.2°. When the left hand was immersed in cold water the flow in the right hand was diminished to 4.71 gm. per 100 cc. per minute for the first two minutes of the immersion, to 3.31 gm. for the next 3 minutes, and it rose only to 4.83 gm. per 100 cc. per minute during the remaining 7 minutes of the period. The vasomotor reflex elicited in the right hand by immersion of the left hand in cold water was accordingly small. When the left hand was immersed in warm water the flow in the right hand sank to 3.46 gm. per 100 cc. per minute for the first 3 minutes of the period. For the next 4 minutes it rose slightly (to 4.42 gm.), for the next 3 minutes to 5.33 gm., and for the remaining 4 minutes of the period to 7.32 gm. per 100 cc. per minute.

It is clear that the initial small flow in the right hand is not due to a vasoconstriction which can either be much increased by immersion

of the contralateral hand in cold water, or much diminished by its immersion in warm water. Even the maximum flow obtained under the influence of the reflex vasodilatation is scarcely half the normal flow in the left hand. Such vasomotor reflex reactions are among the criteria of a circulation diminished by a mechanical block. In the present instance the mechanical block is not extreme, as shown by the ratio of the flows, and therefore reflex vasomotor effects on the flow are still obtainable, although diminished.

There is in any event no probability that irritation of vasoconstrictors by pressure would cause such a great and permanent discrepancy between the blood flows in the two hands. The conclusion was therefore drawn that the deficiency in the circulation of the right hand was due to pressure on the blood supply of the right arm either by the bullet itself, or by the hematoma, or by both. As regards the question whether the flow in the right hand was dangerously small, it could be answered that it was not, and that although, of course, this matter should be tested from time to time, there was no reason to apprehend gangrene with a blood flow of this magnitude.

Five days later another observation was made on the blood flow with the view of determining whether the collateral circulation was increasing. At the time of the second examination the right hand was in much the same condition as at the first examination, only the patient had observed that the finger nails on the right hand were now beginning to grow although not so fast as those on the left hand.

Second Examination.—Pulse 92. Hands in bath at 2.07 p.m., in calorimeters at 2.16½, and out of calorimeters at 2.33.

Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.	Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.
2.16	31.17	31.17		2.26	31.225	31.68	
2.18	31.13	31.22	23.7	2.27	31.24	31.73	22.9
2.19	31.13	31.285		2.28	31.25	31.78	
2.20	31.13	31.34	23.3	2.29	31.27	31.82	
2.21	31.17	31.41		2.30	31.28	31.87	
2.22	31.19	31.48		2.31	31.29	31.91	23.0
2.23	31.20	31.54	23.2	2.32	31.295	31.95	23.1
2.24	31.21	31.595		2.33	31.33	32.00	
2.25	31.22	31.63	23.05	2.42	31.22	31.86	

Cooling of calorimeters in 9 minutes, right 0.11°, left 0.14°. Volume of hands, right 492 cc., left 466 cc. Rectal temperature 37.22°. Water equivalent of calorimeters with contents, right 3,489, left 3,467.

The blood flows in both hands at this examination were somewhat less than on the previous occasion (3.93 gm. per 100 cc. per minute for the right hand, and 10.76 gm. for the left). The ratio, however, between the flows in the two hands was unchanged (1 : 2.74). The room temperature (23° C.) was almost the same as at the first examination. The fact that the ratio of the flows is practically identical with that obtained at the first examination of itself almost precludes the idea that the deficiency in the right hand is due to persistent irritation of vasoconstrictors. A stimulation of this kind could hardly remain constant for 5 days, while a mechanical block might well do so.

The patient was discharged from the hospital soon afterwards.

The blood flow in his hands was again examined on Mar. 8, 1915. Since Nov. 28. 1914, he has been at work and came to the hospital merely for the examination. He says that when he first resumed work, whenever he flexed the forearm on the elbow it was done with a jerk. He finds that the right hand is still weaker than the left and gets tired sooner. There is no pain in it and he uses it freely in his work. He has some little difficulty with the right hand in such movements as those concerned in buttoning his clothes. The right arm is not quite as strong as the left. There is now no pain at the shoulder and no trace of the injury can be detected except a small scar on the right side of the chest at the point of entrance of the bullet, which still remains in the body, no attempt having been made to extract it. The left radial pulse is distinctly stronger than the right. It was not possible to feel the right brachial artery, while the left brachial pulse was strong.

Third Examination.—Hands in bath at 2.50 p.m., in calorimeters at 3.00, and out of calorimeters at 3.15. Pulse 84.

Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.	Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left	Temperature of Room.
2.59	32.03	32.10		3.09	32.26	32.59	23.9
3.01	32.01	32.15		3.10	32.29	32.64	23.9
3.02	32.03	32.20		3.11	32.32	32.695	
3.03	32.04	32.26	23.5	3.12	32.37	32.745	
3.04	32.06	32.31		3.13	32.41	32.795	
3.05	32.10	32.36	24.4	3.14	32.45	32.84	23.8
3.06	32.13	32.42		3.15	32.53	32.88	
3.07	32.18	32.48	24.5	3.33	32.35	32.68	
3.08	32.21	32.53	24.0				

Cooling of calorimeters in 18 minutes, right 0.18°, left 0.20°. Volume of right hand 481 cc., of left 493 cc. Rectal temperature 37.35° C. Water equivalent of calorimeters with contents, right 3,480, left 3,489.

The blood flow in the right hand at this last examination, 110 days after the previous one, was 9.30 gm. per 100 cc. per minute, and in the left hand 11.60

gm., with an average room temperature of 24° C. The sum of the flows in the two hands is only slightly greater than on Nov. 13, 1914 (20.9 gm. as against 20.08 gm.), but the distribution of the blood between the two hands is now very different, the ratio being only 1 : 1.24. Plainly a great improvement has occurred in the interval in the circulation of the right hand.

The volume measurement indicates a considerable increase in the left hand, probably due to work hypertrophy, as he still must use the left more than the right. There is a smaller diminution in the volume of the right hand due, it is to be supposed, either to absorption of a small amount of edema fluid or to slight atrophy. No edema of the hand was observed at any time, but there might have been some increase in tissue liquid not revealed by detectable swelling. The mechanical obstruction on the arterial path which was responsible for the diminished blood flow might, of course, have in some degree involved the venous outflow from the limb as well, although not to such an extent as to cause evident edema. That some pressure was exerted on nerves is indicated by the spasmodic contractions described, but there is no evidence of serious injury to nerves. The slight atrophy may well have been due simply to disuse.

Decided inequalities in the blood flow in the two hands (or feet) not associated with obvious functional or anatomical differences and not conforming to the criteria of inequalities due to a mechanical cause are sometimes observed in clinical cases, particularly, in my experience, in neuropathological conditions. The great characteristic of these inequalities of flow is their instability. Not only does the ratio of the flow in the two hands vary widely in examinations on successive days, without any apparent clinical change to account for the variation, but the ratio may one day be in favor of one hand and the next day in favor of the other, or the two flows, greatly different in amount at one examination, may be found equal at the next. A change in the external conditions (such as a sufficient increase or diminution of the air temperature) which are known to affect the vasomotor system is especially apt to alter or reverse the ratio.

For this reason it is suggested that some vasomotor peculiarity is responsible for the circulatory changes in these cases, and inequalities in the blood flow which possess the criterion mentioned are interpreted as depending on vasomotor rather than mechanical conditions. The results on a typical case (Thomas Q.) will be given.

The patient, a man 36 years of age, when he first came under observation was suffering from alcoholic neuritis affecting particularly the feet. There was no recognizable clinical difference between the two sides. Yet notable differences in the blood flow were made out, which, however, were not stable from

day to day and were therefore interpreted as depending upon vasomotor differences on the two sides not so easily abolished or perhaps more easily produced than in normal persons by the preliminary bath and the subsequent long immersion in the calorimeters. About a year after the first series of examinations the patient was again seen in the hospital, this time suffering from (tubercular) pleurisy with febrile temperature in addition to the neuritis. The change in the clinical picture was very decided and so was the change in the results of blood flow measurements. The marked tendency to cutaneous vasoconstriction already found associated with fever[4] was reflected in a greatly diminished hand and foot flow.

Thomas Q., a railroad clerk, aged 36 years, was admitted to the City Hospital on May 24, 1912, suffering from chronic alcoholism, with alcoholic neuritis. He has been drinking for his entire life. Two years ago he had "alcoholic paralysis" and collapsed while he was walking along the street after being at a dance. His limbs gave way but he did not lose consciousness and resumed his work after four days. His legs swelled and became painful, so he stopped work and went to a hospital. For the past year he has had painful micturition, especially after a drinking bout. In 18 months his weight has declined from 204 to 147 pounds, and his strength has diminished. He has had night sweats at intervals and his appetite has become poor. He has been drinking heavily since March. The legs and feet are equally untrustworthy in walking. He feels no difference between the right and left. The feet feel rather cold to him and recently there has been a tendency for chilblains to form on them. He is nervous. There is tremor of the tongue and lips. The pupils react to light and accommodation. The knee jerk is absent on both sides. There is no special defect of sensation. There is pain on pressure over the nerve trunks of both lower extremities. The upper extremities show nothing special.

On May 29, 1912, the flow in his feet was measured. It came out 1.43 gm. per 100 cc. per minute for the right, and 2.44 gm. for the left (ratio 1 : 1.70), with the rather low room temperature of 21.5°. On May 31 the flow in the right foot was 3.39 gm. per 100 cc. per minute, and in the left foot 3.87 gm. (ratio 1 :1.14), with room temperature 25.4°. These flows are of the normal order of magnitude. Slight and transient reflex diminution of the flow in the left foot was caused by immersion of the right foot in cold water and a marked temporary diminution when the right foot was transferred to warm water. The subsequent increase of flow in the left foot, while the right continued in the warm water, only carried the flow slightly above the initial level. The much smaller flows in the feet on May 29 were probably due to the increased sensitiveness of these cases to vasoconstrictor stimulation occasioned by the considerably lower room temperature, for which there is other evidence. With the increased vasodilatation in both feet on May 31 the difference between them, if of vasomotor origin, would tend to become less.

Two examinations of the hands were made at this time. On June 4, with room temperature 25° C., the flow in the right hand was 8.51 gm. per 100 cc. per minute, in the left 13.20 gm. (ratio 1 : 1.55). The hands were not noticeably affected by neuritis at this time, but later on he returned to the hospital

[4] Stewart, *Jour. Exper. Med.*, 1913, xviii, 372.

with wrist drop in addition to foot drop. The difference in the flow in the two hands on subsequent examination was not found to be permanent, and it was therefore interpreted as due to a functional difference in vasomotor innervation. Immersion of the right hand in warm water caused, after a very slight and transient diminution in the flow (to 9.82 gm. for one minute), one of the greatest reflex increases witnessed in the whole series of observations; *viz.*, to 17.08 gm. per 100 cc. per minute. Immersion of the right hand in cold water was accompanied by a transient diminution in flow in the left hand (to 5.58 gm. per 100 cc. per minute for the first 3 minutes), the flow then increasing to 10.22 gm. per 100 cc. per minute for the remaining 7 minutes, during which the right hand continued in the cold water.

First Examination of Blood Flow.—Thomas Q. Examination of blood flow in the feet, May 31, 1912. Pulse 108. Feet in bath at 2.40½ p.m., in calorimeters at 2.55¼. 3,740 cc. of water in each calorimeter. At 3.13 p.m. the right foot was immersed in cold water at 9° C. He felt it very cold and complained much.

Time.	Temperature of Calorimeters. Right.	Left.	Room	Time.	Temperature of Left calorimeter.	Room.	Notes.
2.54	31.42	31.40		3.22	32.25		
2.57	31.43	31.42	25.3	3.23	32.285	25.5	
2.59	31.50	31.50	25.3	3.24	32.31		
3.01	31.56	31.56		3.25	32.35		
3.03	31.61	31.63	25.3	3.26	32.40		At 3.26 rt. foot put in water at 43° C.
3.05	31.675	31.70		3.27	32.41		
3.06	31.72	31.75		3.28	32.425		
3.07	31.75	31.79	25.4	3.29	32.45		
3.09	31.805	31.86		3.30	32.49	25.7	
3.11	31.88	31.93	25.45	3.31	32.525		
3.13	31.93	32.00		3.32	32.525		Stirring was brief and insufficient.
3.15		32.07		3.33	32.58		
3.17		32.11	25.5	3.34	32.60		Stirring insufficient.
3.18		32.14		3.35	32.635		Foot out of calorimeter.
3.19		32.165		3.44	32.525		Rt. is now at 31.595° C.
3.20		32.21					
3.21		32.23					

Cooling of calorimeters, right 0.335 in 31 minutes, left 0.11 in 9 minutes. Volume of right foot in calorimeter 1,311 cc., of left foot 1,290 cc. Water equivalent of calorimeters with contents, right 4,857, left 4,843. Rectal temperature 37.35°.

Second Examination.—Examination of flow in hands, June 4, 1912. Hands in bath at 2.23 p.m., in calorimeters at 2.33. At 2.47 p.m. the right hand was put into water at 8° C.; at 2.57 into water at 43°. At 3.07 p.m. the left hand was taken out of the calorimeter.

Cooling of calorimeters, right 0.33° in 39 minutes, left 0.13° in 9½ minutes. Volume of right hand 460 cc., of left hand 437 cc. Water equivalent of calorimeters with contents, right 3,463, left 3,445. Pulse 100. Rectal temperature 37.5.

Time.	Temperature of Calorimeters. Right.	Left.	Room.	Time.	Temperature of Left calorimeter.	Room.	Notes.
2.31½	31.57	31.51	24.8	2.52	32.53	24.95	
2.34	31.57	31.53		2.53	32.57		
2.35	31.63	31.62	25.2	2.54	32.605		
2.36	31.695	31.72		2.55	32.635		
2.37	31.74	31.78	25.0	2.56	32.66		
2.38	31.79	31.86		2.57	32.71		
2.39	31.83	31.92		2.58	32.745	25.1	
2.40	31.87	31.96		2.59	32.805		
2.41	31.895	32.02		3.00	32.86		
2.42	31.94	32.08		3.01	32.925	25.1	
2.43	31.995	32.15	25.0	3.02	32.995		
2.44	32.03	32.225		3.03	33.07		
2.45	32.08	32.29		3.04	33.135	25.15	
2.46	32.11	32.34		3.05	33.19		
2.47	32.14	32.38		3.06	33.25		
2.48		32.40		3.07	33.32	25.2	
2.49		32.41		3.16	33.19		Rt. 31.81
2.50		32.43					
2.51		32.48					

That the cause of the inequality between the flows in the two hands observed on June 4, 1912, was a transient functional difference is indicated by the result of the third examination on the following day (June 5). Here with a lower room temperature (22.4°) the flow was reduced in both hands, but far more in proportion in the left (7.31 gm. per 100 cc. per minute for the right, 7.35 gm. for the left hand). The excess in the flow in the left hand is, however, in reality somewhat greater than the numerical results indicate. For the left hand had suffered the loss of a portion of the thumb by amputation a while ago, and the ratio between its surface and its mass was therefore diminished. Also the man is right handed and in right handed persons the flow per 100 cc. of volume is usually somewhat greater than the left.

Third Examination.—June 5, 1912. He says he is feeling well and can walk fairly, although he soon gets tired. He was out on the hospital grounds yesterday and today. Hands in bath at 1.22½ p.m., in calorimeters at 1.32, out of calorimeters at 1.50. Pulse 110.

Time.	Temperature of Calorimeters. Right.	Left.	Room.	Time.	Temperature of Calorimeters. Right.	Left.	Room.
1.31½	31.08	31.05		1.42	31.495	31.39	
1.33	31.07	31.03	22.2	1.43	31.52	31.415	22.4
1.34	31.11	31.07		1.44	31.575	31.45	
1.35	31.175	31.12	22.3	1.45	31.61	31.49	22.4
1.36	31.21	31.15		1.46	31.64	31.52	
1.37	31.27	31.20	22.4	1.47	31.69	31.55	
1.38	31.31	31.24		1.48	31.72	31.59	22.4
1.39	31.39	31.30		1.49	31.76	31.625	
1.40	31.425	31.335		1.50	31.785	31.635	
1.41	31.47	31.36		1.58	31.665	31.525	

Cooling of calorimeters in 8 minutes, right 0.12°, left 0.11°. Volume of right hand 468 cc., of left hand 436 cc. Water equivalent of calorimeters with contents, right 3,469, left 3,444. Rectal temperature 37.7°.

Thomas Q. was discharged from the hospital on June 29, 1912, and was re-admitted on Jan. 19, 1913. He has been drinking for 4 weeks and is decidedly worse than at the previous admission. He cannot walk at all and has wrist drop of both hands. He first noticed the wrist drop the day he came. In both extremities the extensor muscles are more involved than the flexors. The nerve trunks are tender, the reflexes absent. He was treated by hot baths and massage of the extensor muscles. He states that if he is made to sit around even a few minutes after the bath he gets a severe chill lasting 20 to 30 minutes, which does not occur if he is put straight to bed. He never has a chill except after the hot bath. This is of interest as it corresponds with the evidence of increased susceptibility to reflex vasoconstriction of the cutaneous blood vessels deduced from the blood flow examinations. The flow in the hands was examined on May 21 and again on May 24, 1913, and the flow in the feet on May 24. At this time he had some fever and on May 29 the physical signs of pleurisy were found. On June 15 and again on June 18, 1913, tubercle bacilli were found in the sputum, and he was sent to the sanitarium on June 24.

When examined on May 21, 1913, nearly a year after the first examination, the blood flow in the right hand was found to be only 4.49 gm. per 100 cc. of hand per minute, and in the left hand 3.06 gm. (ratio 1 : 1.46), with the relatively high room temperature of 26.4° C. These flows were for the last 12 minutes in the calorimeters. His rectal temperature was much above the normal (40.45° C.), and the tendency to vasoconstriction associated with fever is no doubt a factor in the small flow. This tendency is illustrated by the tardiness with which the rate at which the thermometers rose became steady. Three days later (on May 24, 1913) the flow in the hands was still smaller (2.31 gm. per 100 cc. per minute for the right hand and 2.26 gm. for the left hand, for 12 minutes in the calorimeters before the testing of the vasomotor reaction, with room temperature 23.2° C.). Calculated for the last 7 minutes of this period the flows were only 1.71 and 1.58 gm. per 100 cc. per minute for the right and left hands respectively, denoting a great tendency to the onset of vasoconstriction. A rapidly increasing vasoconstriction revealed by a decrease in the rate of heat loss to the calorimeters has been observed in other cases of fever; for instance, in pneumonia before the rapid rise of body temperature. In one case in which the condition had not as yet revealed itself clearly by the physical signs, this behavior of the hands in the calorimeters suggested the onset of fever, the temperature rose nearly 5° F. within eight hours, and the next day physical signs of pneumonia were present.

During immersion of the right hand in warm water, the flow in the left, far from being increased, was actually diminished (to 1.31 gm. per 100 cc. per minute), a further illustration of the increasing vasoconstriction, which cannot be overcome by the reflex vasodilatation normally associated with immersion of the contralateral hand in warm water. The patient felt worse than at the last examination.

The flow in the feet was also abnormally small (0.84 gm. per 100 cc. per

minute for the right foot, and 0.87 gm. for the left for a period of 20 minutes in the calorimeters, with room temperature 23.3° C.). For the last 10 minutes of this period the flows were only 0.77 and 0.72 gm. per 100 cc. per minute for the right and left foot, respectively, showing that the vasoconstriction was increasing in the feet also with the duration of immersion. Naturally with a tendency to vasoconstriction manifested so strongly in both hands and feet, the ratio of foot to hand flow (1 : 2.6) lies within the normal limits, whereas with a lesser degree or less general distribution of the vasoconstriction this ratio is apt to be markedly disturbed in favor of the hand flow.

Cases do occur, although in my experience quite rarely, in which without any obvious reason a marked inequality in the flow in the two hands is present and persists indefinitely, without reversal of the ratio. The ratio, however, is unstable, varying greatly from day to day, and this differentiates the condition from inequalities of mechanical origin and places it in the vasomotor group. This condition is illustrated in the case of William F.

William F., a laborer, aged 50 years, was admitted to the Gity Hospital on March. 22, 1912, suffering from "combined system disease." His illness began last June with difficulty in walking, and this has become rapidly worse. Sometimes he almost falls. About three months before admission he had a severe nose-bleed lasting for three nights without known cause. For the past year he has suffered from severe frontal headache lasting from six to twenty-four hours. He also complains of pain in the pit of the stomach coming on after eating. No vomiting. He sweats much at night, and the sweats are followed by chills. The sweating is so copious that his gown is soaked in five minutes. He says he used to be "hot-blooded," wearing no overcoat in winter, but now he is always chilly. His feet get cold as ice in bed. His hands also get cold now, although not so readily as the feet. When he goes to bed at night his feet are apt to be swollen, but the swelling is all gone in the morning. He had chancre twenty years ago and it was not treated. He is married but never had any children. His wife had two or three miscarriages. He does not drink or chew tobacco. He walks with a spastic gait. Knee jerks exaggerated. and ankle clonus can be elicited on both sides. There is some toe drop on the left side. He says he has pain all the time in his "bones," in the legs and back, but not much pain in the arms. There seems to be some loss of sensation in the left leg, and he cannot always tell the difference between warmth and cold there. Pain perception is prompt, and vibration sense good. His power of localization is somewhat impaired. He can stand with his eyes closed. Both pupils react normally to light. No obvious wasting of the hands. The grip of both hands is fairly good, the right somewhat stronger than the left. He can not write now, although a well educated man. Blood count on Mar. 24, 1912, erythrocytes 5,480,000, leucocytes 7,400. Mar. 29. Wassermann test negative. Apr. 17, spinal fluid clear. Cell count 6 per cc. X-ray examination negative. Urine, nothing special. Heart examination negative. The blood flow in the

hands was examined on Apr. 24, 1912, and that in the hands and feet the following day (Apr. 25).

First Examination of Blood Flow.—William F. Apr. 24, 1912. Hands in bath at 2.43 p.m., in calorimeters at 2.52. At 3.15 p.m. left hand put into water at 44° C. Pulse 100. Mouth temperature 36.65°. At 3.29 left hand put in water at 8° C. At 3.41 left hand put in water at 43° C. At 3.48 hand out of calorimeter.

Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.	Time.	Temperature of Right calorimeter.	Temperature of Room.	Time.	Temperature of Right calorimeter.	Temperature of Room	Notes.
2.51	30.52	30.55		3.16	30.79	23.5	3.38	31.46		
2.53	30.47	30.50	22.3	3.17	30.80		3.39	31.49		
2.54	30.47	30.49		3.18	30.81		3.40	31.50		
2.55	30.47	30.49		3.19	30.84		3.41	31.505		
2.56	30.46	30.48		3.20	30.88		3.42	31.52		
2.57	30.46	30.47		3.21	30.915		3.43	31.525		
2.59	30.45	30.46		3.22	30.975	22.2	3.44	31.53	22.25	
3.00	30.45	30.455		3.23	31.02		3.45	31.54		
3.01	30.455	30.455	22.5	3.24	31.08		3.46	31.55		
3.03	30.48	30.45		3.25	31.105		3.47	31.56		
3.04	30.50	30.44		3.26	31.15		3.48	31.57		
3.05	30.52	30.435		3.27	31.195	22.0	3.56½	31.46		Lt. 30.40
3.06	30.54	30.445	22.5	3.28	31.24					
3.07	30.58	30.44		3.29	31.295					
3.08	30.60	40.44		3.30	31.305					
3.09	30.63	30.435		3.31	31.32					
3.10	30.67	30.435		3.32	31.335					
3.11	30.695	30.445		3.33	31.35	22.0				
3.12	30.705	30.445		3.34	31.365					
3.13	30.73	30.45		3.35	31.38					
3.14	30.75	30.455		3.36	31.40					
3.15	30.78	30.45		3.37	31.43					

Cooling of calorimeters, right 0.11° in 8½ minutes, left 0.41° in 41½ minutes. Volume of right hand, 517 cc., of left hand 523 cc. Water equivalent of calorimeters with contents, right 3.509, left 3,513. Rectal temperature 37.4° C.

On Apr. 24 the flow in the right hand came out 4.20 gm. per 100 cc. per minute; in the left, 1.11 gm. (ratio 1 : 3.78), with room temperature 22.5°, an average flow much below the normal. Immersion of the left hand in warm water caused a good contralateral vasomotor reflex, indeed considering the long duration of the vasodilatation, an exaggerated one. The vasodilatation was preceded in the normal way by a good vasoconstriction for the first 3 minutes of immersion of the left hand. The diminution of the flow in the right hand on immersion of the left in cold water was also prompt, substantial, and durable.

The next day the flow in the right hand was 5.83 gm., in the left 3.11 gm. (ratio 1 : 1.87), with room temperature 23.5°, still a marked preponderance in favor of the right hand.

In the feet the flow was remarkably small but the relative preponderance in the right foot was precisely the same as in the right hand, the ratio of the flow

in the right hand to that in the right foot being 15 : 1, and the corresponding ratio for the left hand and foot also 15 : 1. Immersion of the left foot in warm water caused, if anything, a diminution of the flow in the right foot, but the change was insignificant.

The patient was discharged from the hospital at his own request on May 12, and readmitted on May 31, 1913. On June 6, 1912, the blood examination showed hemoglobin 85 per cent., leucocytes 11,800. He says his legs now get red if rubbed or scratched and feel "burning." This was not the case when he was in the hospital before. He describes the heat as coming "from the inside of the legs, from the bone." Neither the legs nor the feet feel warm to the observer's hand. The veins of the legs are larger than before. He does not sweat much now. The knee jerk is still exaggerated, and ankle clonus can be elicited. He is less able to walk than when previously in the hospital and must use a stick, which was not the case before. Romberg's sign is not present. He has had much trouble in urination for over a year, with burning pain in the penis. In the sitting position he can easily make water, but not standing up. The pulse in the left brachial is distinctly smaller than in the right. This is easier to make out than any difference between the two radials. He was discharged from the hospital "unimproved," Oct. 6, 1912. The blood flow in the hands was examined on June 11, and that in the feet on June 12, 1912.

Second Examination.—June 11, 1912. Hands in bath at 2.16 p.m., in calorimeters at 2.26¼, and out of calorimeters at 2.50.

Time.	Temperature of			Time.	Temperature of		
	Calorimeters.		Room.		Calorimeters.		Room.
	Right.	Left.			Right.	Left.	
2.25	31.50	31.40	24.5	2.39	31.65	31.43	
2.27	31.47	31.36		2.40	31.665	31.43	24.7
2.28	31.48	31.355	24.5	2.41	31.68	31.435	
2.29	31.49	31.355		2.42	31.695	31.44	
2.30	31.50	31.36	24.6	2.43	31.715	31.45	
2.31	31.515	31.365		2.44	31.73	31.455	
2.32	31.535	31.375		2.45	31.755	31.465	24.8
2.33	31.56	31.395		2.46	31.78	31.49	
2.34	31.595	31.40	24.8	2.47	31.80	31.51	
2.35	31.60	31.41		2.48	31.815	31.52	24.7
2.36	31.61	31.42		2.49	31.83	31.525	
2.37	31.625	31.425	24.7	2.50	31.85	31.53	
2.38	31.64	31.425		3.04	31.69	31.39	

Cooling of calorimeters in 14 minutes, right 0.16°, left 0.14°. Volume of right hand 493 cc., of left 499 cc. Water equivalent of calorimeters with contents, right 3,489, left 3,494. Rectal temperature 37.6°.

On June 11 the flow in the right hand was 4.40 gm., in the left 2.77 gm. (ratio 1 : 1.58) with room temperature 24.7° C. On June 12 the flows were 0.82 and 0.48 gm. in the right and left foot, respectively. Immersion of the right foot in warm water caused practically no change in the left foot. The foot flows are still abnormally small, although larger than on Apr. 25. It is to be remarked,

however, that the ratio between the flow in the right hand and that in the right foot (5.4 : 1) is again almost the same as the ratio between the flow in the left hand and that in the left foot (5.3 : 1). In other words, the relative preponderance of flow is almost the same in the right foot as in the right hand. The blood flow in the right hand and foot in this patient is therefore, it would appear, permanently and decidedly greater than in the left hand and foot, although at the time of examination no marked clinical difference in the condition of the two sides of the body could be detected. The variability in the ratio between the flows in the two hands from time to time, in the absence of material variations in the factors which determine general vasomotor changes (*e. g.*, decided changes in the external temperature), differentiates the condition from an inequality due to a mechanical cause and stamps it apparently as a functional peculiarity.

The curious fact that when the ratio between the flows in the two hands varies, the ratio between the flows in the two feet varies to the same amount, would seem to require for its explanation the assumption that the intensity of the vasomotor innervation of one-half of the body, or at least of the extremities on one side, is simultaneously affected and to the same degree with respect to the innervation of the other half. Changes in the bulb, for example in its circulation, affecting the "general vasomotor center," not necessarily exclusively on one side, but to a greater degree on one side than on the other, might be expected to produce such an effect. If the change responsible for the phenomenon were located below this level it would seem that the whole dorsolumbar region from which the vasoconstrictor outflow takes place would require to be subjected to it. Is there here, perhaps, an indication of a somewhat greater progress of the pathological change on one side than on the other, a difference which has not as yet otherwise revealed itself? If the primary lesion in this case is in the upper motor neurone, it is not unnatural to suppose that the vasomotor reflex arcs may maintain an even increased vasoconstrictor tone associated with a relatively small peripheral blood flow corresponding to the exaggeration of the skeletal reflexes and the spasticity of the skeletal muscles.

A marked variability in the ratio of the blood flows in the two hands (or feet) in our observations on normal persons has not been seen. But in one normal case a decided permanent difference in the flows in the two hands was made out, the ratio of the flows remaining practically constant in observations made at an interval of 3 days and varying surprisingly little even over long periods.

In John R., a normal man, at that time 20 years old, the flow on Mar. 22, 1913, in the right hand was 10.08 gm., and in the left 7.25 gm. per 100 cc. per minute, with room temperature 24.0° C. for a period of 13 minutes, the ratio of the flows being 1 : 1.39. On Mar. 25, 1913, the flows were 12.38 and 8.82 gm., respectively, for the right and left hands (ratio 1 : 1.40) with room temperature 24.8° C. for a period of 15 minutes. On Nov. 14, 1914, the flows were 14.85 gm. for the right hand and 10.07 gm. per 100 cc. per minute for the left hand

for a period of 22 minutes, with room temperature 24.3° C. (ratio 1 : 1.47). There is no anatomical or functional difference between the two hands or arms, nor any history of injury which would explain such a difference in the blood flow. The stability of the ratio is strongly in favor of a mechanical explanation, a congenital difference in the cross-section of the two subclavians, for example, rather than an explanation based on a difference on the two sides in the permanent vasomotor tone or a difference in the reflex vasomotor reaction to the manipulations and external conditions connected with the measurements. No such difference was found in the foot flows, the ratio being 1 : 1.05 in the supine and 1 : 1.13 in the sitting position on Mar. 25, 1913, with room temperatures 25.1° and 24.6°, respectively. It was at first supposed that some as yet latent unilateral pathological process, for instance pulmonary tuberculosis, might be connected with the anomaly, but nothing has developed to justify that suggestion. The subject stated at the time of the last examination that the tendency to free bleeding from slight injuries and especially from the nose, from which he had suffered for 15 years, has now disappeared.[5]

John R. Nov. 14, 1914. Hands in bath at 11.42 a.m., in calorimeters at 11.55, out of calorimeters at 12.08 p.m.

Time.	Temperature of Calorimeters. Right.	Left.	Room.	Time.	Temperature of Calorimeters. Right.	Left.	Room.
11.54	32.12	32.22	24.1	12.08	32.67	32.51	
11.56	32.12	32.22		12.09	32.70	32.53	
11.57	32.16	32.24	24.2	12.10	32.75	32.555	24.3
11.58	32.20	32.255		12.11	32.79	32.58	
11.59	32.23	32.27		12.12	32.82	32.62	24.3
12.00	32.285	32.305	24.3	12.13	32.88	32.64	
12.01	32.32	32.32		12.14	32.91	32.66	
12.02	32.38	32.35		12.15	32.94	32.67	24.4
12.03	32.42	32.37		12.16	32.97	32.68	
12.04	32.48	32.40	24.3	12.17	32.995	32.69	
12.05	32.52	32.43		12.18	33.02	32.695	24.3
12.06	32.56	32.45		12.28	32.88	32.555	
12.07	32.61	32.48	24.3				

Cooling of calorimeters, right and left 0.14°, in 10 minutes. Volume of right hand 387 cc., of left hand 357 cc. Water equivalent of calorimeters with contents, right 3,405, left 3,381. Rectal temperature 36.64° C. Pulse 62. Blood pressure, right arm 98 (systolic), 84 (sudden change in sound), 76 (cessation of sound). Another observation 98, 83, 74. Left arm 97, 79, 65.

Note Added May 7, 1915.—On this day, which was close and muggy, the flow in the right hand was 18.52 gm. and in the left 14.01 gm. (ratio 1 : 1.32) with room temperature 25.1° C.

As a practical point of technique it may be suggested that when it is desired to test the stability of the ratio between the flows on the

[5] Stewart, *Jour. Exper. Med.*, 1913, xviii, 354.

two sides, in cases where the question arises whether the cause is a nervous or a mechanical one, this could perhaps often be quickly done by measuring the blood flow several times on the same day with considerably different room and calorimeter temperatures. If the inequality is of vasomotor origin, it may be expected to disappear or be greatly reduced in one or more of the sets of observations, whereas an inequality due to a permanent mechanical cause could not disappear.

SUMMARY.

1. In cases in which great inequalities in the blood flow in the two hands were produced by mechanical causes (ligation or compression of vessels, embolism), the stability of the ratio of the flows, in successive measurements at short intervals, was found to be characteristic. Over long intervals the opening up of collateral circulation or the progressive increase of the block (in a case of multiple embolism with thrombosis) was followed by changes in the ratio of the blood flows in the normal and the affected part. Another criterion of these conditions was found to be that the inequality was not abolished by producing general vasomotor changes; *e. g.*, by altering the external temperature.

2. In certain cases inequalities in the blood flow in the two hands (or feet) were found which were not stable from day to day, and which could be abolished, reduced, increased, or reversed by alterations in the external conditions which bring about general vasomotor changes. These inequalities, not associated with clinically recognizable differences between the parts compared, were interpreted as due to unequal activity of the vasomotor mechanism on the two sides. The condition appeared to be most frequent in certain groups of neurological cases.

I wish to express my obligations to the staff of the City Hospital and to my colleagues at Lakeside Hospital for many courtesies.

TABLE I.

Date.	Case.	Age.	Pulse rate.	Blood pressure.	Temperature (C.) of: Room.	Art'l blood.	Calorimeters. Right.	Calorimeters. Left.	Volume of part in cc. Right.	Volume of part in cc. Left.	Heat given off in gm.-cal. Right.	Heat given off in gm.-cal. Left.	In min.	Blood flow in gm. per min. Right.	Blood flow in gm. per min. Left.	Flow per 100 cc. of part per min. Right.	Flow per 100 cc. of part per min. Left.	Notes.
Oct. 26, 1914	Costa B...	47 yrs.	102	114.85	22.0	36.95	31.81	31.42	473	441	1980	424	15	28.53	5.67	6.03	1.28	Hands } Embolism of lt. hand and rt. leg.
					22.0	36.85	31.68	31.99	1191	1188	1040	1946	15	14.90	29.67	1.25	2.50	Feet
Feb. 24, 1915			81	110.75	23.8	37.05	32.07	31.86	498	452	1711	690	11	34.70	11.48	6.96	2.54	Hands.
Feb. 26, 1915			102		24.0	37.35	31.82	31.45	497	457	2469	900	10	49.60	16.95	9.98	3.70	Hands.
					23.5	37.25	31.87	32.71	1132	1199	694	5847	18	7.96	77.95	0.70	6.50	Feet.
Nov. 13, 1914	Walter L..	25 yrs.			23.3	36.92	31.22	31.77	503	464	2063	4769	15	26.80	68.59	5.32	14.76	Hands. Bullet in rt. shoulder.
					23.1	....	31.44	....	....	....	234	....	2	23.72	....	4.71	....	Lt. hand in water at 8.2° C.
					23.2	....	31.48	....	....	....	245	....	3	16.68	....	3.31	....	Lt. hand still in cold water.
					23.1	....	31.56	....	....	....	821	....	7	24.31	....	4.83	....	Lt. hand still in cold water.
					23.3	....	31.65	....	....	....	248	....	3	17.42	....	3.46	....	Lt. hand in water at 44° C.
					23.3	....	31.69	....	....	....	420	....	4	22.26	....	4.42	....	Lt. hand still in warm water.
					23.3	....	31.76	....	....	....	374	....	3	26.84	....	5.33	....	Lt. hand still in warm water.
					23.3	....	31.86	....	....	....	671	....	4	36.83	....	7.32	....	Lt. hand still in warm water.
Nov. 18, 1914			92	R. 115.80	23.0	36.72	31.22	31.67	492	466	1246	2964	13	19.36	50.16	3.93	10.76	Hands.
Mar. 8, 1915				L. 130.80	24.0	36.85	32.30	32.60	481	493	2015	2407	11	44.73	57.20	9.30	11.60	Hands.
May 29, 1912	Thomas Q.	36 yrs.	84		21.5	36.50	30.67	30.80	1265	1262	1708	2846	18	18.08	30.82	1.43	2.44	Feet. Alcoholic neuritis.
May 31, 1912			108		25.4	36.75	31.68	31.71	1311	1290	3250	3630	16	44.51	50.01	3.39	3.87	Feet.
					25.5	....	....	31.98	....	....	....	1119	6	....	43.44	....	3.36	Rt. foot in water at 9° C.
					25.5	....	....	32.18	....	....	....	1501	7	....	52.13	....	4.04	Rt. foot still in cold water.
					25.7	....	....	32.31	....	....	....	238	2	....	29.78	....	2.30	Rt. foot in water at 43° C.
					25.6	....	....	32.43	....	....	....	1405	7	....	51.62	....	4.00	Rt. foot still in warm water.
June 4, 1912			100		25.0	37.00	31.86	31.95	460	437	2355	3410	13	39.16	57.71	8.51	13.20	Hands.
					25.0	....	....	32.40	....	....	....	303	3	....	24.39	....	5.58	Rt. hand in water at 8° C.
					25.0	....	....	32.57	....	....	....	1247	7	....	44.68	....	10.22	Rt. hand still in cold water.
					25.1	....	....	32.73	....	....	....	165	1	....	42.93	....	9.82	Rt. hand in water at 43° C.
					25.1	....	....	33.03	....	....	....	1240	9	....	74.66	....	17.08	Rt. hand still in warm water.
June 5, 1912			110		22.4	37.2	31.43	31.33	468	436	3330	2879	17	34.23	32.05	7.31	7.35	Hands.

TABLE I.—*Concluded.*

Date.	Case.	Age.	Pulse rate.	Blood pressure.	Temperature (C.) of				Volume of part in cc.		Heat given off in gm.-cal.			Blood flow in gm. per min.		Flow per 100 cc. of part per min.		Notes.
					Room.	Art'l blood.	Calorimeters. Right.	Calorimeters. Left.	Right.	Left.	Right.	Left.	In min.	Right.	Left.	Right.	Left.	
May 21, 1913	Thomas Q.		140		26.4	39.95	31.43	31.35	400	379	1656	1077	12	17.99	11.59	4.49	3.06	Hands. Much worse. Has fever.
May 24, 1913			116	.85.60	23.2	40.1	31.24	31.20	393	372	869	810	12	9.08	8.42	2.31	2.26	Hands.
					23.5	.....	31.28	.....	....	....	409	....	10	5.15	.....	1.31	.....	Lt. hand in water at 44° C.
					23.3	40.0	30.91	30.86	1063	1057	1460	1520	20	8.92	9.23	0.84	0.87	Feet.
Apr. 24, 1912	Wm. F....	50 yrs.	100		22.5	36.9	30.62	30.45	517	523	1719	474	14	21.72	5.83	4.20	1.11	Hands. Combined degeneration.
					23.5	.....	30.80	.....	....	....	228	....	3	13.84	.....	2.67	.....	Lt. hand in water at 44° C.
					22.1	.....	31.05	.....	....	....	2193	....	11	37.86	.....	7.32	.....	Lt. hand still in warm water.
					22.0	.....	31.34	.....	....	....	561	....	6	18.68	.....	3.61	.....	Lt. hand in water at 8° C.
					22.0	.....	31.44	.....	....	....	702	....	6	23.81	.....	4.60	.....	Lt. hand still in cold water.
					22.2	.....	31.54	.....	....	....	544	....	7	16.11	.....	3.11	.....	Lt. hand in water at 43.4° C.
Apr. 25, 1912			104		23.5	36.9	30.78	30.63	493	502	2058	1188	13	28.74	15.64	5.83	3.11	Hands.
					22.4	36.8	30.42	30.35	1370	1265	742	366	24	5.38	2.62	0.39	0.21	Feet.
					22.1	.....	30.32	.....	....	....	262	....	10	4.49	.....	.....	0.32	Lt. foot in water at 43° C.
June 11, 1912					24.7	37.1	31.76	31.48	493	499	1046	699	10	21.76	13.82	4.40	2.77	Hands.
June 12, 1912			108		23.4	36.85	30.82	30.73	1360	1317	855	492	14	11.25	6.38	0.82	0.48	Feet.
					23.6	.....	.....	30.68	....	....	....	369	10	.....	6.64	.....	0.50	Rt. foot in water at 43° C.
Nov. 14, 1914	John R....	22 yrs.	62	98.75	24.3	36.14	32.57	32.46	387	357	4065	2620	22	57.50	35.95	14.85	10.07	Hands.

Studies on the Circulation in Man

XIII. THE BLOOD FLOW IN THE HANDS AND FEET IN CERTAIN DISEASES OF THE NERVOUS SYSTEM

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CLEVELAND

STUDIES ON THE CIRCULATION IN MAN

XIII. THE BLOOD FLOW IN THE HANDS AND FEET IN CERTAIN DISEASES OF THE NERVOUS SYSTEM *

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CLEVELAND

The study of the blood flow in the hands and feet is of special interest in diseases of the nervous system, in which the extremities are so often involved. The skeletal reflexes are so frequently affected that it seemed of some consequence to explore also the vasomotor reflexes by the method described in previous papers.[1] A preliminary account of some of the work was given in a Harvey Lecture.[2] The material available of course allowed a more complete study of some conditions than of others. Also, in a first survey, those conditions were naturally selected in which changes in the blood flow or in the vascular reflexes seemed most likely to be detected, and if detected to be capable of being most clearly related to the symptoms and morbid anatomy of the diseased states. Such conditions as affected only one side (hemiplegia, unilateral peripheral neuritis) were obviously of interest not only in connection with the pathologic physiology of the circulation, but also as affording the opportunity of testing still further the technic of the method, since they permitted the direct comparison of a normal part with the corresponding diseased part.

For one or other of these reasons it happens that most of the material studied in this paper falls under one of three heads: (1) Peripheral neuritis (due to trauma, rheumatism, alcohol, etc.); a case or two in which the condition was probably neuralgia rather than neuritis is included in this group; (2) cerebral hemorrhage (or obstruction of cerebral vessels) with hemiplegia, and (3) tabes. Some other cases are also introduced mainly for the sake of comparison. These comprise cases of motor neuron disease, cerebral tumor, and gunshot wound of the brain. Some observations, chiefly on the vascular reflexes, were made on patients affected by certain poisons which act especially on the nervous system (alcohol, lead), but in whom at the time of observation no symptoms of actual anatomic lesions (peripheral neuritis) were present. A case of excessive tobacco smoking and a

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* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. Paper II of this series, Heart, 1911, iii, 76; Papers IX, X and XI, The Archives Int. Med., 1913, xii, 678; Ibid., 1914, xiii, 1, 177.
2. Nov. 23, 1912.

patient recovering from tetanus under treatment with antitoxin are also included because the vasomotor reflexes seemed to present points of interest. In one or two instances the blood-flow measurements were applied to the detection of malingering with, it is thought, helpful or at least suggestive results.

PERIPHERAL NEURITIS

In three cases of unilateral brachial neuritis, not of long standing, in which no decided atrophy of the hand had as yet occurred, although the strength of the grip was markedly diminished, the blood flow in the affected hand was conspicuously greater than in the contralateral normal hand. In two of these cases the lesion was on the right side and as has been mentioned in previous papers, normal right-handed persons usually show a slight preponderance in blood flow per 100 c.c. of hand volume on the right side. In the cases referred to, however, the difference was much greater, and one of the cases in which the lesion was on the left side presented an equally large excess in the left hand.

Thus in O. A. H., a man with right brachial neuritis probably of traumatic origin, and not at the time of observation associated with any wasting in the right hand, the flow in the right hand was 8.79 grams and in the left hand 6.99 grams per 100 c.c. of hand per minute, with room temperature 24 C. The ratio of the flows in the two hands (1:1.26) shows a very decided preponderance of flow in the affected hand.

O. A. H., a house carpenter aged 60, was admitted to the dispensary January 25, suffering from right brachial neuritis. Seven years ago he fell from a building on his right shoulder and has always had some pain in shoulder since. For three months he had severe pain and weakness in his shoulder. Pain is felt on pressure over the circumflex and over the median nerve above the elbow, and tenderness over the brachial plexus in neck and axilla. The grip of the right hand is much less strong than that of the left. Slight numbness is the only sensory disturbance. All movements of the right arm are weak, but there is no wasting of the hand. February 24: The systolic blood pressure is 130. No impairment of tactile sensation exists and warmth and cold sensibility is good. Pain sensation is diminished below the elbow. On April 26 his arm was better. The blood flow in the hands was examined January 12, before admission. Hands in bath at 3 p. m.; in calorimeters at 3:10 p. m.; removed from calorimeters at 3:26. 3,050 c.c. of water were in each calorimeter. Room temperature 24.1 C.

In Casimir M., a man aged 27, with left brachial neuritis, the blood flow in the right hand was 5.63 grams, and in the left hand 7.40 grams per 100 c.c. per minute, with an average room temperature of 21.9 C. The ratios of the flows in the two hands is 1:1.31, indicating a great excess in favor of the left hand. The case may fairly be considered an "early" one. Although there was some wasting of the muscles of the left upper arm, and some weakening of the grasp of the left hand,

little if any wasting of the hand as revealed by the volume measurement could be detected.

TABLE 1.—Calorimetric Measurements in Case of O. A. H.

Time	Right	Left	Time	Right	Left
3:00	29.98	29.87	3:21	30.43	30.18
3:12	30.00	29.89	3:22	30.50	30.25
3:13	30.03	29.91	3:23	30.57	30.30
3:14	30.09	29.94	3:24	30.63	30.36
3:15	30.13	29.97	3:25	30.71	30.41
3:16	30.20	30.01	3:26	30.78	30.48
3:17	30.23	30.02	3:35	30.68	30.40
3:19	30.32	30.10	3:51	30.52	30.26
3:20	30.38	30.13			

Cooling of calorimeters in twenty-five minutes, R., 0.26 C., L., 0.22 C. Volume of right hand in calorimeter, 445 c.c. of left 425 c.c. Pulse 80.* Mouth temperature 37.1 C. Room temperature 23.9. He is right handed.†

* Except when otherwise mentioned the pulse rate was always taken in a sitting position.

† It is to be assumed that a patient is right handed unless the contrary is stated.

Casimir M. was admitted to the dispensary, January 4, with left brachial neuritis. He had noticed pain in the left elbow for three months, mostly when at work (as a sewing machine operator). He had had no injury. No local signs were seen at elbow. There was no history of venereal infection. Considerable thickening of the radial artery existed. On January 31 the left arm was still weak and he could not use it properly at work, while there was distinct atrophy of some of its muscles. The circumference of the left upper arm was 24.5 cm., that of right upper arm 26.5 cm., of left forearm 25 cm., and of right 26 cm. Pain on pressure was felt over some of the cervical nerves on the left side, but no pain on pressure over the arm. The grasp of the left hand was weaker than that of the right. On February 17 he felt much better. The blood flow in the hands was examined January 31.

The hands were put into the bath at 3:38½ p. m., into the calorimeters at 3:51, taken out of calorimeters at 4:08. 3,050 c.c. of water were in each calorimeter. Pulse 68. Mouth temperature 36.6 C.

TABLE 2.—Calorimetric Measurements in Case of Casimir M.

Time	Right	Left	Room	Time	Right	Left	Room
3:50	29.40	29.36		4:01	29.58	29.58	
3:52	29.39	29.35	21.7	4:02	29.61	29.62	
3:54	29.42	29.41		4:03	29.64	29.65	
3:55	29.44	29.42		4:04	29.68	29.71	
3:56	29.45	29.43		4:05	29.71	29.75	
3:57	29.47	29.43	22.1	4:06	29.76	29.81	
3:58	29.49	29.48		4:07	29.78	29.83	21.9
3:59	29.52	29.51		4:08	29.80	29.86	
4:00	29.55	29.53		4:27	29.56	29.63	

Cooling of calorimeters in nineteen minutes, R., 0.24 C., L., 0.23 C. Volume of right hand 400 c.c., of left hand 370 c.c.

In John S., a man with right brachial neuritis and distinct weakening although no definite wasting of the right hand, the flows were 10.29 grams and 7.66 grams per 100 c.c. per minute in the right and

left hands respectively, with room temperature 22.3 C. The ratio of the flows (1:1.34) denotes a great preponderance of flow in the hand affected by the lesion. On immersion of the left hand in cold water the flow in the right sank to 5.18 grams per 100 c.c. per minute for the first four minutes and then rose to 8.16 grams per 100 c.c. per minute for the remaining five minutes of the period of immersion. On immersing the left hand in warm water the flow in the right hand mounted to 10.16 grams, which was scarcely equal to the initial flow. This indicates that the flow in the right hand at the beginning of the observation was probably already associated with a considerable vasodilatation on which it was easy to impose a decided reflex vasoconstriction but not an additional vasodilatation.

John S., a bricklayer aged 45, was admitted to the dispensary on February 27 with neuritis in the right arm. He had had pain in right elbow for four weeks, unaccompanied by heat or swelling, and the arm had lost strength. The grip of the right hand was much weaker than that of the left. Tenderness was felt over the external condyle, and very slight tenderness over the right brachial plexus. He attributed the condition to cold. March 6, his condition was the same. The blood flow in the hands was examined February 27.

The hands were put into the bath at 2:50 p. m., into the calorimeters * at 3. removed from calorimeters at 3:37. At 3:15 the left hand was immersed in water at 9 C., and at 3:24 in water at 43 C. At 3:31 the left hand was dried and wrapped up. Pulse 74. Mouth temperature 36.74 C.

TABLE 3.—Calorimetric Measurements in Case of John S.

Time	Right	Left	Room
2:59½	29.61	29.50	
3:02	29.69	29.55	23.3
3:03	29.72	29.59	
3:04	29.78	29.63	
3:05	29.84	29.67	
3:06	29.90	29.71	
3:07	29.96	29.75	
3:08	30.02	29.83	23.4
3:09	30.09	29.88	
3:10	30.16	29.92	
3:11	30.21	29.96	
3:12	30.28	30.03	
3:13	30.33	30.06	
3:14	30.39	30.11	22.8
3:15	30.45	30.15	
3:16	30.48		
3:17	30.50	.....	23.3
3:18	30.52		
3:19	30.53		
3:20	30.57		
3:21	30.61		
3:22	30.66		
3:23	30.69		
3:24	30.73		
3:25	30.77	.....	23.3
3:26	30.81		
3:27	30.87		
3:28	30.91		
3:29	30.97		
3:30	31.02		
3:31	31.08		
3:32	31.11		
3:33	31.14		
3:34	31.19	.....	22.9
3:35	31.23		
3:36	31.27		
3:37	31.30		
3:43	31.22	29.91	

Volume of right hand 412 c.c., of left hand 402 c.c. Cooling of calorimeters, R., 0.08 C. in six minutes, L., 0.24 C. in twenty-eight minutes.

The most natural explanation of the preponderance in the flow on the side of the lesion is that the vasoconstrictor fibers are involved in the neuritis, with a resultant diminution of the vasomotor tone of the hand. It is difficult to see how a neuritis due to trauma or to pressure

* As always, unless otherwise stated, the quantity of water in each hand calorimeter was 3,015 c.c.

could fail to affect these fibers. Nor is there any evidence that they escape completely in other forms of peripheral neuritis although, until it is eliminated by proof to the contrary, the possibility must be granted that a particular poison may spare the efferent vasomotor fibers in the peripheral nerves which it attacks. In a peripheral neuritis involving the vasocontrictors these need not of course be totally incapable of conduction any more than the motor fibers of the part. In the case of John S., for example, it is evident they were not completely paralyzed, since a good reflex vasoconstriction was obtained when the contralateral hand was put into cold water. There is some indication, however, that such a reflex, even when of as great an initial intensity as normal, may be more fleeting than under normal conditions, perhaps because the partially degenerated fibers or their endings are sooner fatigued.

In a fourth case, that of Kaspar J., a man suffering from "early" unilateral brachial neuritis apparently of rheumatic origin, a similar disproportion between the flows in the two hands was noticed, the preponderance being, as before, in favor of the affected hand. Later on, however, in this case practical equality in the flows in the two hands was observed, either because the improvement in the condition had progressed so far at the second examination that the vasomotor tone of the affected hand had again become normal, or possibly because of the action of the salicylates with which he was being treated. At the first examination the flow in the hand on the side of the neuritis (the right) was 4.80 grams per 100 c.c. per minute (allowing for the swelling of the hand) and in the left 3.58 grams, the ratio being 1:1.34, with room temperature 24.2 C. These flows are subnormal, which may of course be due to the man's general condition, recovering as he was from an acute illness (rheumatic fever). The heart was probably to some extent handicapped. Also arteriosclerosis was present, which is always associated with a subnormal hand flow.[3]

At the second examination with a somewhat higher room temperature (25.3 C.) the flow was practically the same in the left hand (3.72 grams) but in the right hand it was reduced almost to equality with that in the left (3.76 grams per 100 c.c. per minute). The fact that the flow in the left hand remained so low in spite of the relatively high room temperature seems to indicate a great tendency to vasoconstriction. If this were the case we should expect that the preponderance of flow previously observed in the right hand, which by hypothesis was due to diminution, though not to paralysis, of vasoconstrictor tone, should tend to disappear. The slight tendency to vasodilatation is indicated clearly by the tests of the vasomotor reflexes. During immer-

3. Paper XI of this series, The Archives Int. Med., 1914, xiii, 177.

sion of the left hand in warm water the flow in the right sank to 2.68 grams per 100 c.c. per minute for the first four minutes of immersion and only reached 4.12 grams per 100 c.c. per minute for the remaining seven minutes. For the first three minutes of immersion of the left hand in cold water the flow in the right was 2.74 grams and for the remaining six minutes 3.75 grams per 100 c.c. per minute. The marked slowing of the pulse rate (57 per minute as compared with 92 at the previous examination), in spite of the higher room temperature and the unchanged body temperature, may be associated with the tendency to peripheral vasoconstriction.

Kaspar J., a laborer, aged 50, was admitted to Lakeside Hospital, April 12, with rheumatic fever. Two weeks before, he began to have severe pain in the left ankle and knee, later in the right knee. Five days before admission the right elbow, wrist, and later the shoulder began to trouble him. The heart sounds were clear; the pulse regular in rate, but irregular in amplitude. The vessel wall was palpable. On April 20 the legs were well, but the right upper arm was still sensitive and much atrophied. On April 30 there was very little pain, but movement of the right arm was much impaired; analgesia existed over the entire right arm. The blood flow in the hands was examined May 5 and again May 8. The grip of the right hand was still weak; pain was felt over the right brachial plexus. Convalescence was uninterrupted and he was discharged May 12.

The hands were put into the bath at 2:36½ p. m., into the calorimeters at 2:46½. At 2:56½ the left hand was put into water at 43 C. At 3:04 the left hand was put into water at 9.5 C. He felt the cold water painful. At 3:13 the right hand was removed from the calorimeter. Pulse 92. Mouth temperature 36.7.

TABLE 4.—First Blood Flow Examination of Kasper J.

Time	Right	Left	Room
2:45	29.65	29.56	
2:48	29.67	29.57	
2:49	29.69	39.60	
2:50	29.71	29.62	
2:51	29.75	29.63	
2:52	29.78	29.64	
2:53	29.80	29.67	
2:54	29.84	29.70	
2:55	29.88	29.72	24.2
2:56	29.90	29.74	
2:57	29.93	29.76	
2:58	29.965		
2:59	29.95	.....	24.2
3:00	30.03		
3:01	30.07		
3:02	30.095	.....	24.25
3:03	30.13		
3:04	30.175		
3:05	30.20	.....	24.4
3:06	30.215		
3:07	30.24		
3:08	30.28		
3:09	30.31		
3:10	30.34	.....	24.4
3:11	30.37		
3:12	30.40		
3:13	30.44		
3:21	.....	29.57	
3:22	30.34		

Volume of right hand 511 c.c., of left 457 c.c. The right hand is still somewhat swollen and noticeably larger than the left. Cooling of calorimeters, R., 0.10 C. in nine minutes, L., 0.19 C. in twenty-four minutes.

The particulars of the second examination of Kasper J. are given in the general table.

In a fifth case (John McH.), although symptoms described by the patient suggested a right brachial neuritis, the suspicion of malingering could not be excluded. The flow in the right hand was 4.30 grams

and in the left 3.91 grams per 100 c.c. per minute with room temperature at 23.3 C. The ratio of the flow of the two hands is 1:1.1. On the following day another examination was made and the flows came out 5.46 grams and 4.74 grams for the right and left hands respectively with the same room temperature, a ratio of 1:1.15. Immersion of the left hand in warm water caused a marked vasoconstriction in the right hand for the first six minutes, reducing the flow to 3.23 grams per 100 c.c. per minute. This was succeeded by a moderate vasodilatation (for the remaining seven minutes of the period of immersion of the left hand) the flow in the right hand increasing to 6.11 grams.

John McH., a laborer, aged 58, was admitted to the City Hospital, June 4, apparently suffering from right brachial neuritis. He complained of stinging and numbness of right forearm and hand, especially the middle finger. He had been addicted to alcohol and had several attacks of delirium tremens. There was pain on pressure over the right shoulder, at the inner side and front of the head of the humerus. He could raise his right arm slowly and apparently with some pain to the horizontal position but not higher. His hands felt cold. He said he was cold all over. He stated that he sometimes had sudden swelling of the back of the right hand, which disappeared in a few minutes. He had no trouble in walking but said he was "very irritable and twitched a great deal." There seemed to be a considerable mental factor in the case and a possibility of malingering. The pain and tingling did not inconvenience him, but he feared they might be premonitory of a "stroke." Blood flow in hands was examined on June 5 and again on June 6. Particulars of the first blood-flow examination are given in the general table.

TABLE 5.—Calorimetric Measurements in Second Examination of John McH.

Time	Right	Left	Room
2:40	31.40	31.31	
2:42	31.39	31.31	
2:43	31.40	31.32	
2:44	31.41	31.33	23.1
2:45	31.425	31.35	
2:46	31.46	31.375	
2:47	31.49	31.41	23.1
2:48	31.52	31.425	
2:49	31.54	31.44	23.2
2:50	31.575	31.46	
2:51	31.59	31.48	
2:52	31.60	31.49	23.2
2:53	31.625	31.52	
2:54	31.66	31.54	
2:55	31.68	31.55	23.4
2:56	31.71	31.58	
2:57	31.75	31.625	
2:58*	31.78	31.635	23.2
2:59	31.795	31.65	
3:00	31.80	31.66	
3:01	31.835	31.695	
3:02	31.85	31.71	23.15
3:03	31.88	31.72	
3:04	31.88	.....	22.9
3:05	31.89		
3:06	31.90		
3:07	31.91		
3:08	31.925	.....	22.9
3:09	31.935		
3:10	31.965		
3:11	31.99	.....	23.05
3:12	32.02		
3:13	32.045		
3:14	32.075		
3:15	32.09	.....	23.0
3:16	32.12		
3:39	31.82	31.29	

Cooling of calorimeters, R., 0.30 C. in twenty-three minutes, L., 0.43 C. in thirty-six minutes. Rectal temperature 37.5 .C. Volume of right hand 512 c.c., of left 491 c.c. Water equivalent of calorimeters with contents, R., 3,504, L., 3,488. Blood pressure left arm, systolic 116, 93 (sound gone). Right arm, 115, 93.

* Here he heard warm water ordered and became anxious.

At the second examination the patient says the pain in the right shoulder is rather worse than yesterday. The hands were placed in bath at 2:32 p. m., in the calorimeters at 2:41½, taken out of calorimeters at 3:16. Pulse 88. At 3:03 left hand was put into water at 43 C.

While it would of course be absurd to claim that such observations would of themselves be sufficient to justify a diagnosis of malingering in this case the slight difference in the flows in the two hands, scarcely exceeding if at all that often observed in normal persons, suggested that if the symptoms described were genuine they were due rather to a functional than to a structural lesion—to a brachial neuralgia rather than to an "early" brachial neuritis. In the period during which the patient was still under observation the condition did not develop further and he was discharged "improved" a very few days after the last examination. There is little doubt that in cases in which certain neurologic conditions are simulated a measurement of the blood flow might sometimes help to clear up the diagnosis. In long-standing paralyses whether due to a peripheral or to a central lesion there is a decided diminution in the blood flow of the affected hand (or foot) as compared with the normal part.

Thus, in a case of long-standing brachial neuritis of the right side associated with cervical rib (Mrs. M. C.) the flow was much smaller in the affected than in the normal hand (3.98 grams per 100 c.c. per minute in the right, and 5.70 grams in the left hand) the ratio being 1:1.43, with room temperature 23.5 C.). This agreed with the statement of the patient that the right hand was always colder than the left. There was slight wasting of the right hand, only clearly revealed by measurement of the volume, but the hand was little used. The atrophy chiefly affected the proximal segments of the limb. Here it may be supposed that the nerve lesion has led to anatomic changes in the blood vessels causing a narrowing of their lumen.[4]

Mrs. M. C., aged 38, was admitted to the dispensary in April, 1910. She states that in her fourteenth year she worked very hard in a hayfield on a hot day, had sunstroke and fell unconscious. When she recovered consciousness, right arm and shoulder were aching and there was some loss of power there. This has gone on gradually increasing. Continuous pains have been in the right shoulder for the past three weeks. There is exostosis of the scapula (curved scapula) and a marked prominence in right supraclavicular region extending upward and forward for two inches and pressing on the brachial plexus. Cervical ribs were shown by Roentgen ray. Extreme tenderness was felt on pressure in supraclavicular region. Atrophy and weakness were noted of the serratus magnus, infraspinatus, supraspinatus, and latissimus dorsi. The deltoid and other muscles of the arm and forearm show weakness and slight atrophy. There was no apparent wasting of the right forearm or hand, although she does not now use them much. The grip of the right hand was fairly strong, although weaker than the left. She was right handed. There

4. Todd: Jour. Nerv. and Ment. Dis., 1913, xl, 439.

was a marked diminution of sensation to pricking and to contact with camel's hair brush over right shoulder. Over arm and forearm sensation is normal. Blood flow in hands was examined Feb. 14, 1911.

Hands in bath at 2:03 p. m., were placed in calorimeters at 3:14, and taken out of calorimeters at 3:29. Pulse 88. Mouth temperature 37.4 C. Room temperature 23.8 C.

TABLE 6.—CALORIMETRIC MEASUREMENTS IN CASE OF MRS. M. C.

Time	Right	Left
3:13	30.29	30.27
3:16	30.27	30.27
3:17	30.29	30.31
3:18	30.30	30.33
3:19	30.31	30.34
3:20	30.33	30.38
3:21	30.35	30.41
3:22	30.36	30.43
3:23	30.38	30.46
3:24	30.39	30.48
3:25	30.40	30.50
3:26	30.41	30.51
3:27	30.42	30.52
3:28	30.43	30.55
3:29	30.44	30.57
3:54	30.21	30.34

Cooling of the calorimeters in twenty-five minutes, 0.23 C. Volume of right hand 295 c.c., of left hand 301 c.c.

The possibility of distinguishing a neuralgia from an "early" neuritis by measurement of the blood flow seems to be indicated by such cases as that of Max B., a carpenter, aged 24, in whom the diagnosis of occupational neuralgia (possibly with slight neuritis) was made.

The blood flow came out 13.89 grams per 100 c.c. per minute for the right (the affected) hand and 13.38 grams for the left, with room temperature 24.5 C. (ratio of flows in the two hands 1:1.04). These flows are of a normal order of magnitude for the age and general condition of the patient and the room temperature. The slight preponderance of flow in the right hand is no more than that usually observed in normal right-handed persons. If the condition were a typical "early" neuritis a much greater excess of flow in the affected hand would be expected, owing to paralysis of vasoconstrictors. The vasoconstrictor reflex in the right hand when the left was immersed in cold water was well marked, the flow falling to 7.25 grams for the first three minutes of immersion, but rising again during the remaining six minutes to 10.83 grams per 100 c.c. per minute. Immersion of the left hand in warm water caused a moderate increase in flow in the right (to 12.53 grams per 100 c.c. per minute for the whole period of immersion of seven minutes). The initial value was not reached. The vasomotor reflex to warmth in this experiment differed from that in normal cases and also from that in the cases of undoubted neuritis in this respect, that there was no distinct initial diminution of flow in the right hand when the left was put into the warm water, or a very slight and transient one. There is not enough material, however, to show whether this has any general significance. The protocol of the case has already been published.[5]

5. Cleveland Med. Jour., 1911, x, 398.

One case diagnosed as sciatica of the left leg was examined.

Frank S., a man aged 64, a laborer in a stable, had to sleep about the stable, often on the wet floor. For six weeks previous to admission the leg had been growing rapidly worse. Now he can hardly bear his weight on it. The trouble is worse at night. Both knee-jerks are exaggerated, especially the left. The Achilles jerk is evident on the left side. Some tenderness is present along the nerve trunks of the left leg, which feels cold at times.

At the first examination of the blood flow—three days after admission when the condition was still acute—the flow in the feet was found exceedingly small both absolutely and in proportion to the hand flow, namely, 0.22 gram per 100 c.c. per minute for the right foot, and 0.47 gram for the left, with room temperature 21 C. Immersion of the right foot in warm water caused no increase in the flow in the left foot, which for ten minutes during immersion of the right foot continued at the rate of 0.43 gram per 100 c.c. per minute. The flow in the right hand was 4.20 grams, in the left 4.39 grams, with room temperature 22.1 C. The ratio of the combined foot flows to the combined hand flows was 1 :12.4, indicating a marked tendency to vasoconstriction in the feet, possibly due in part to the pain. The fact that in spite of this tendency to vasoconstriction the flow in the left foot is double that in the right would seem to indicate a condition of the nerves of the left leg constituting a partial block for vasoconstrictor impulses. If a condition of neuritis of the large nerve trunks of the leg is present this would agree with the results on cases of brachial neuritis. Twenty-two days later, when the pain in the thigh had disappeared, the flow in the left foot was found somewhat inferior to that in the right, which agreed with the fact that for three or four days previous to the examination he had felt the left foot cold, although it was covered with sweat.

A number of cases of alcoholic neuritis came under observation. A detailed account of the results in one will suffice. A second case is considered in another connection in Paper XII, published in *Journal of Experimental Medicine,* xxii, 1915, No. 1.

Charles de M., a pianist, aged 29, height 6 feet, 1 inch, weight 170 pounds, was admitted to the City Hospital, July 9, with diagnosis of chronic alcoholism with neuritis. He has been drinking since boyhood and drinks a quart of whisky daily. There is no noticeable anemia. The heart and lungs are normal. The liver is palpable. Knee-jerk and tendo Achillis reflex are markedly exaggerated. A musculo-spiral paralysis of the left forearm and wrist with well-marked wrist drop is present. There is tenderness but no atrophy. The left hand is weaker than right; the left foot is also worse than the right. Two months ago there was marked toe-drop in the left foot. He could stand on the right foot alone but not on the left. The toe-drop is not now so bad. A general tremor exists. The maximum temperature on July 11 was 100.6 F. After this it was never above 99.6 F. with a minimum of 97.8 F. The patient sweats freely. He was discharged improved, July 29. The blood flow in the hands

was examined on July 10 and in the feet and hands on July 16. He was unable to walk into the room.

First examination, July 10: Hands in bath at 1:58½ p. m., in calorimeters at 2:08½. At 2:25 the right hand was put into water at 8.1 C., and at 2:35 into water at 43.1 C. He complained much of the cold water. At 2:44 the right hand was taken from the calorimeter. Pulse 68. The day was very warm.

TABLE 7.—Calorimetric Measurements in Case of Charles de M.

Time	Right	Left	Room
2:07	31.325	31.32	30.1
2:09½	31.37	31.36	
2:10	31.39	31.39	
2:11	31.46	31.45	30.2
2:12	31.505	31.525	
2:13	31.57	31.60	
2:14	31.63	31.68	
2:15	31.685	31.75	
2:16	31.75	31.81	30.1
2:17	31.81	31.86	
2:18	31.87	31.93	
2:19	31.94	32.01	
2:20	32.00	32.05	
2:21	32.065	32.125	30.0
2:22	32.125	32.18	
2:23	32.19	32.26	
2:24	32.26	32.32	
2:25	32.31	32.365	30.0
2:26½	.....	32.42	
2:27	.....	32.425	
2:28	.....	32.45	
2:29	.....	32.49	
2:30	.....	32.55	29.9
2:31	.....	32.60	
2:32	.....	32.64	
2:33	.....	32.695	
2:34	.....	32.73	29.8
2:35	.....	32.77	
2:36	.....	32.815	
2:37	.....	32.85	
2:38	.....	32.90	29.8
2:39	.....	32.945	
2:40	.....	32.995	
2:41	.....	33.04	
2:42	.....	33.10	
2:43	.....	33.14	
2:44	.....	33.20	29.7
2:50	32.17	33.11	

Cooling of calorimeters, R., 0.14 C. in thirty-four minutes, L., 0.09 C. in fifteen minutes. Volume of right hand 488 c.c., of left hand 479 c.c. Rectal temperature 37.5 C. Water equivalent of calorimeters with contents, R., 3,485, L., 3,478. Blood pressure left arm, systolic 118 (palpation), 121 (stethoscope), 74 (sound gone).

Second examination, July 16: The patient's left hand is to-day in a splint on account of wrist-drop. It feels stiff and swollen, probably from the pressure of the splint. He walked into the room without help and feels much better. Hands in bath at 3:07 p. m., were in calorimeters at 3:17, and out of calorimeters at 3:29. Pulse 84. The weather is much colder than at the last examination.

TABLE 8.—Calorimetric Measurements in Second Examination of Charles de M.

Time	Right	Left	Room
3:15	31.40	31.39	24.9
3:18	31.425	31.405	25.2
3:19	31.495	31.465	
3:20	31.56	31.51	25.15
3:22	31.66	31.60	
3:23	31.72	31.66	
3:24	31.79	31.71	
3:25	31.83	31.77	
3:26	31.90	31.805	25.1
3:27	31.95	31.855	
3:28	31.99	31.89	
3:29	31.035	31.935	
3:35	31.96	31.86	

Cooling of calorimeters in six minutes, R., 0.075 C., L., 0.075 C. Volume of right hand 479 c.c., of left hand 494 c.c. Water equivalent of calorimeters with contents, R., 3,478, L., 3,490. Rectal temperature 37.7 C.

At the first examination in Charles de M. the flow in the right hand was 9.96 grams per 100 c.c. per minute, in the left (the weaker of the two hands) 10.76 grams, with the very high room temperature 30.1 C. The ratio between the flows in the two hands was 1:1.08. These flows

are subnormal for his age at this room temperature. Immersion of the right hand in cold water caused a good reflex vasoconstriction, the flow in the left dropping to 5.84 grams per 100 c.c. per minute for the first three minutes, to rise again to 9.45 grams per 100 c.c. per minute for the next seven minutes of the immersion. Immersion of the right hand in warm water caused only a very moderate increase above the initial flow in the left hand (to 11.27 grams).

At the second examination, six days later, the flow was 9.92 grams for the right hand and 8.95 grams for the left with room temperature 25.1 C. These flows are fairly normal for the room temperature, and the patient's condition was much better than at the previous examination. His pulse rate was 84 instead of 68. The deficiency in the flow in the left hand is probably to be attributed to obstruction caused by a splint. But in no patient with alcoholic neuritis examined has the same marked difference between the two hands (or feet) been observed as in the cases of brachial neuritis already described. Two points have to be considered in this relation—first, in alcoholic neuritis the action of the poison is necessarily bilateral, although the neuritis may at a particular time have progressed farther on the one side than on the other. Secondly, if, as appears often to be the case, it is the small muscular branches which are specially affected in alcoholic neuritis, a very marked increase in the blood flow of the hand most affected by the neuritis could scarcely be expected, since the hand flow is above all a cutaneous blood flow.

The flow in the feet at the second examination of Charles de M. came out 0.90 gram per 100 c.c. per minute for the right foot and 1.20 grams for the left. These flows are not only absolutely small, but small in proportion to the hand flows. The preponderance is on the side (left) on which the foot-drop is worse, but in dealing with such small flows, particularly in the case of the feet in which vasoconstriction caused by the necessary manipulations connected with the measurement is not easily avoided in patients specially susceptible to this condition, too much stress must not be laid on small differences. The next case, although the patient was much addicted to alcohol, probably represents a neuritis due to pressure.

Frank D., aged 39, height 5 feet, 11 inches, a school teacher in Germany, since then a casual laborer, was admitted to the City Hospital, July 22, with wrist-drop of left hand. Pronation and supination are perfect. He can palmarflex left hand to some extent but cannot dorsiflex it. He has long been a heavy drinker and has had delirium tremens. Has been sleeping outside. On the morning of July 21 he first noticed that he could not move his left hand. For all he knows he may have been lying on it. He never had anything of the kind before. Some numbness is present on the dorsum of the left hand, especially on the radial side, although pin pricks and contact of the blunt point are felt everywhere. Wrist-jerk is absent on the left side, but is well marked on the right. Knee-jerk is present on both sides. The heart and lungs are normal.

There is no noticeable anemia. He was discharged improved July 27. The blood flow in the hands was examined July 23.

The hands in bath at 1:54 p. m., were in calorimeters at 2:06. Left hand out of calorimeter at 2:47. The right hand was put into cold water (8 C.) at 2:23 p. m. Pulse 76. At 2:34 right hand was put into water at 43 C.

TABLE 9.—Calorimetric Measurements in Case of Frank D.

Time	Right	Left	Room
2:05	31.01	30.97	
2:07	31.025	30.985	
2:08	31.06	31.01	
2:09	31.095	31.05	25.1
2:10	31.14	31.08	
2:11	31.19	31.11	25.2
2:12	31.235	31.165	
2:13	31.30	31.23	
2:14	31.38	31.29	
2:15	31.43	31.36	25.2
2:16	31.505	31.43	
2:17	31.57	31.49	
2:18	31.635	31.565	
2:19	31.70	31.635	
2:20	31.78	31.72	
2:21	31.84	31.79	25.2
2:22	31.91	31.86	
2:23	31.95	31.94	
2:24	.....	31.97	
2:25	.....	31.995	
2:26	.....	32.01	
2:27	.....	32.05	
2:28	.....	32.075	25.1
2:29	.....	32.13	
2:30	.....	32.17	25.05
2:31	....	32.24	
2:32	.....	32.28	
2:33	.....	32.325	
2:34	.....	32.35	25.15
2:35	.....	32.365	
2:36	.....	32.37	
2:37	.....	32.38	
2:38	.....	32.395	25.25
2:39	.....	32.405	
2:40	.....	32.45	
2:41	.....	32.50	
2:42	.....	32.56	
2:43	.....	32.61	
2:44	.....	32.665	25.2
2:45	.....	32.72	
2:46	.....	32.78	
2:47	.....	32.845	
3:06	31.53	32.62	

Cooling of calorimeters, R., 0.46 C. in forty-three minutes, L., 0.225 C. in nineteen minutes. Volume of right hand, 572 c.c., of left hand 542 c.c. Water equivalent of calorimeters with contents, R., 3,553, L., 3,529. Rectal temperature 37.6 C. Blood pressure left arm systolic 133 (palpation), 133 (stethoscope), 86 (sound gone). Another observation 133, 87.

In the case of Frank D. a slight preponderance of flow in the left hand was observed, 10.18 grams per 100 c.c. per minute for the right hand and 10.54 grams for the left with room temperature 25.2 C. for the last 11 minutes before testing the vasomotor reaction. The ratio of the flows in the two hands is 1:1.03. Immersion of the hand in cold water caused a good and durable vasoconstriction in the left hand. Immersion of the right hand in warm water occasioned a great initial vasoconstriction in the left, lasting for three minutes, during which the flow was reduced to 3.38 grams per 100 c.c. per minute. This gave way suddenly, as is normally the case, to vasodilatation, the flow in the left hand reaching 10.81 grams per 100 c.c. per minute for the remaining eight minutes of immersion of the right in the warm water. It will be observed that the initial flow was only slightly surpassed.

Since in this case the paralysis is confined to one hand, no other part of the body being at all affected, and since it came on suddenly, the conclusion seems justified that it was a pressure palsy. It is known that the long supinator sometimes escapes in pressure paralysis of the musculo-spiral nerve. Obviously cutaneous nerves are only slightly involved, and vasomotor fibers for the cutaneous vessels would not in

this case be affected to any appreciable extent. Moreover it has been stated that the radial nerve does not carry vasomotor fibers.[6]

Although this statement is probably based on too slight an experimental foundation and need not be taken literally, it is clear enough that in the case under consideration a difference in the flow in the two hands comparable to that observed in lesions affecting the brachial plexus could not be expected.

In a case of motor neuron disease without sensory deficiency (Mrs. Mary N.) the vasoconstrictor reflexes were found to be of quite normal intensity and of more than normal duration.

Mrs. Mary N., a tailoress, height 5 feet, 6 inches, aged 46, was admitted to the dispensary, Nov. 10, 1910, suffering from progressive muscular atrophy. Her left hand became very painful about September, 1909. About a month thereafter she noticed some atrophy of the thenar eminence and weakness of the hand. About Christmas, 1909, the right hand became similarly affected. The condition gradually progressed and now the right arm shows some atrophy of the deltoid and musculo-spiral paralysis in the forearm, and wrist-drop with some median paralysis as well. Some atrophy of the thenar eminence exists. On the left side there is atrophy of the thenar eminence and some weakness of flexors and extensors but no wrist-drop. No loss of reflexes is shown in either arm. Both wrists and hands are wasted. The grip of both hands is very weak. The left leg is smaller than right, and has been so, at any rate, from the age of 3. It shows peroneal palsy with foot-drop and shortened Achilles tendon, yet she can walk well. Some pain is present along the spine at the base of the neck. Knee-jerk and Achilles reflex are exaggerated on the right side, absent on the left. Babinski's sign is noted in the left foot. There is no sensory disturbance, clonus, or Romberg's sign. The pupils react to light and accommodation. The blood gives a strongly positive Wassermann reaction. The spinal fluid shows 150 cells per c.c., practically all mononuclear. The Noguchi reaction is positive. Physical examination of thorax is negative. Treatment with mercurials and potassium iodid, also with salvarsan, was without result. The patient continued to come to the dispensary till January, 1913, her condition gradually growing worse.

On March 7, 1912, the blood flow in the hands was examined. Hands in bath at 2:27½ p. m., in calorimeters at 2:38. At 2:52 the right hand was put into water at 8 C. At 3 p. m. right hand was put into water at 43 C., which caused the hand to tingle. At 3:07 right hand was dried and wrapped in warm cloth. At 3:14 right hand was removed from calorimeter. Pulse 116. Mouth temperature 37.6 C.

The blood flow in the right hand was 6.99 grams, and in the left 7.13 grams per 100 c.c. per minute with room temperature 23.6 C. Immersion of the right hand in cold water caused the flow in the left to fall to 3.70 grams. There was no increase during the whole time for which the right hand continued in the cold water (seven minutes). The vasoconstriction was therefore intense and durable. When the right hand was immersed in warm water the flow in the left was further diminished to 3.37 grams. The intensity and persistence of the reflex vasoconstriction in this case may pretty safely be taken to indi-

6. Simons, A.: Arch. f. Anat. u. Physiol., 1910, 559.

cate that the lesion in the motor neurons has not extended to the vasomotor cells in the cord or to the efferent paths from them. Since the pathologic change appears to be a system disease affecting the motor neurons but sparing the sensory neurons, there is nothing strange in its avoiding the vasomotor neurons also.

TABLE 10.—Calorimetric Measurements in Case of Mrs. Mary N.

Time	Right	Left	Room
2:37½	29.62	29.61	
2:39	29.60	29.58	23.6
2:40	29.64	29.61	
2:41	29.69	29.64	
2:42	29.72	29.69	
2:43	29.78	29.73	
2:44	29.82	29.78	24.0
2:45	29.86	29.82	
2:46	29.89	29.86	
2:47	29.92	29.90	
2:48	29.97	29.93	
2:49	30.00	29.96	
2:50	30.04	30.00	23.3
2:51	30.07	30.03	
2:52	30.10	30.06	
2:53	.....	30.07	23.3
2:54	.....	30.09	
2:55	.....	30.11	
2:56	.....	30.12	
2:57	.....	30.13	
2:58	.....	30.14	
2:59	.....	30.16	
3:00	.....	30.17	
3:01	.....	30.18	
3:02	.....	30.20	
3:03	.....	30.22	
3:04	.....	30.22	
3:05	.....	30.24	
3:06	.....	30.24	23.9
3:07	.....	30.25	
3:08	.....	30.28	
3:09	.....	30.30	
3:10	.....	30.33	
3:11	.....	30.36	
3:12	.....	30.37	
3:14	.....	30.39	
3:15	29.85		
3:36	29.64	30.16	

Cooling of calorimeters, R., 0.25 C. in twenty-tree minutes, L., 0.23 C. in twenty-two minutes. Volume of right hand 340 c.c., of left hand 320 c.c.

Another case (Stanislas C.) in which a more or less general atrophy of the extremities, especially the anterior, existed presents certain interesting features. On account of the low degree of intelligence of the patient and his defect of speech the history of the case could not be clearly ascertained. Nor could the defects of sensation which seemed to exist be properly studied. Although this increased the difficulty of making a diagnosis and the true nature of the case was not cleared up, it will not be unprofitable, it is hoped, to quote the blood-flow findings, since they seemed capable of suggesting something toward the diagnosis and of supplementing precisely in such circumstances the examination of the sensory condition.

Stanislas C., a Polish laborer, aged 32, height 5 feet, 6 inches, was admitted to Lakeside Hospital, April 5. The patient complains that he cannot talk properly. Seven months before he was hit by a brick and has since been unable to swallow or talk. He did not lose consciousness. The right supraclavicular region shows a scar from the middle of the clavicle to the top of the scapula. The pupils react promptly to light and accommodation. The mouth tends to be drawn to the right. The tongue protrudes to the right and shows a fine tremor. The soft palate hangs to the right, and the left arch is higher than the right. Blood pressure, 124 systolic, 76 diastolic. General atrophy of muscles of extremities is shown. There is some contracture of the fingers of the right hand. No edema exists. Atrophy is noted of the muscles of the neck; the trapezius, splenii, levator scapulae and serrati. His gait is shuffling but not ataxic. There is no hypotonus of the thigh. All the deep reflexes are exaggerated, except those of the right arm, in which the biceps, triceps and supinator reflexes are gone. There is ankle clonus, but no Babinski or Kernig's sign. Romberg's sign is

very slight. The abdominal and cremasteric reflexes are increased. The right arm is smaller than the left, but the volume measurement showed the left *hand* somewhat atrophied in comparison with the right. Paresis is apparent of the left facial muscles. When asked to smile, the mouth is drawn to the right, but when made to laugh spontaneously both sides are equally used. The right side of the forehead wrinkles more than the left. The vocal cords move very poorly. Then sense of taste is disturbed. His intelligence is very low and does not permit satisfactory examination of sensation. He says that all sensations (temperature, pain, touch, vibration) are better felt over the right side (arm, leg and trunk) than over the left. It is doubtful whether this is true.

The blood flow in the hands was examined April 19. Hands were in bath at 2:25 p. m., in calorimeters at 2:39. Mouth temperature 36.8 C. Pulse 72. At 2:50½ p. m. the left hand was immersed in water at 12 C. At 2:55½ p. m. the left hand was dried and wrapped up. At 2.59⅙ p. m. the left hand was put into water at 43.5 C. At 3:06 the left hand was put into water at 9 C. At 3:13 left hand was dried and wrapped up. At 3:17 right hand was removed from calorimeter.

TABLE 11.—Calorimetric Measurements in Case of Stanislas C.

Time	Right	Left	Room	Time	Right	Left	Room
2:38	29.90	29.93		3:00	30.80	.....	23.5
2:40	29.91	29.89	23.7	3:01	30.87		
2:41	29.94	29.90		3:02	30.94		
2:42	29.97	29.89		3:03	30.99	.....	23.6
2:43	29.99	29.90		3:04	31.07		
2:44	30.02	29.90		3:05	31.12		
2:45	30.07	29.90	23.8	3:06	31.18		
2:46	30.10	29.91		3:07	31.22	.....	23.7
2:47	30.17	29.91	23.6	3:08	31.27		
2:48	30.21	29.91		3:09	31.32		
2:49	30.25	29.92	23.6	3:10	31.39		
2:50	30.30	29.92		3:11	31.45		
2:51	30.35	.....	23.8	3:12	31.49		
2:52	30.39			3:13	31.56	.....	23.6
2:53	30.43			3:14	31.60		
2:54	30.49	.....	23.7	3:15	31.65	.....	23.5
2:55	30.57			3:16	31.70		
2:56	30.60			3:17	31.77	.....	23.5
2:57	30.65			3:17½	.....	29.68	
2:58	30.71	.....	23.6	3:28	31.63	29.60	
2:59	30.78						

Cooling of calorimeters, R., 0.14 C. in eleven minutes, L., 0.32 C. in thirty-eight minutes. Volume of right hand in calorimeter 486 c.c., of left hand 422 c.c.

The flow in the right hand came out 7.0 grams and in the left only 1.47 grams per 100 c.c. per minute (for six minutes before the vasomotor test) the greatest difference between the two hands which has been observed in the whole series of observations. Measurement showed that the left hand was atrophied in comparison with the right. On immersing the left hand in cold water (for four minutes) the flow in the right increased to 7.85 grams per 100 c.c. per minute. When the left hand was dried and wrapped up, the flow in the right hand rose to 9.55 grams, to increase further to 10.28 grams on immersion of the left hand in warm water. A subsequent immersion of the left hand in cold water produced no effect on the flow unless to keep it stationary, and when the left hand was again wrapped up the flow in the right increased to 10.88 grams. These anomalous results in the reflex vaso-

motor tests have scarcely any parallel in our series of observations. The most obvious explanation would be that the left hand was insensitive to cold, and the entire passivity of the patient when the hand was immersed in water at 9 C., which usually produces some discomfort, lends support to the suggestion. The initial vasoconstriction produced by immersion of the contralateral hand in warm water was also absent in this case, and again the suggestion is plausible that the left hand was insensible to warmth. The steady increase in the flow of the right hand during the whole course of the vasomotor tests would then be due simply to a spontaneously increasing vasodilatation unaffected by impulses from the left hand. While it would be rash to lay stress on isolated observations of this kind, it may be further pointed out that the marked deficiency of the blood flow in the left hand as compared with the right would agree well with a suggestion made when the diagnosis was being considered, that the general condition was superposed on an old left-side hemiplegia. For as we shall see directly, in the hemiplegias examined there was always a deficiency in blood flow in the paralyzed hand. The paresis of the left side of the face would also fit in with this. On the other hand the apparent absence of reflex vasomotor response in the right hand when the left was immersed in warm or cold water would agree with another suggestion made, that a syringomyelia (of the bulb) existed. In any case it seems reasonably clear that in circumstances in which the subjective response of the patient to warmth and cold cannot be studied information might be obtained by an objective method, namely, the study of the vasomotor reflex response.

HEMIPLEGIA

In the four cases of hemiplegia examined the flow in the paralyzed hand was always inferior to that in the normal hand. In C., a man aged 57, with hemiplegia of nine years' standing (paralysis of the left side of the face, left arm and leg) from which there had been very little recovery, the flow in the right hand was 9.15 grams and in the left only 4.67 grams per 100 c.c. per minute, with room temperature 22.2 C. During immersion of the right hand in warm water the flow in the left was 4.31 grams per 100 c.c. per minute for a period of nine minutes, and exactly the same during immersion of the right hand in cold water for a period of seven minutes. In this case there was no question of any defect of conduction in the afferent segment of the reflex vasomotor arc, since it was the normal hand which was subjected to the warmth and cold stimulation, and these sensations were perfectly perceived. The absence of the vasomotor reflex in this old-standing paralysis was interpreted as probably due to anatomic changes in the vessels of the atrophied left hand, including changes in the efferent

vasomotor nerves of the hand and their terminations. The protocol of the case has already been published.[7] In the other cases of hemiplegia in which the vasomotor reflexes were examined, evidence was obtained of the activity of the vasomotors of the paralyzed hand, reflex vasoconstriction, however, predominating over reflex vasodilatation.

Mrs. Eva M., aged 56, was admitted to the City Hospital, Sept. 11, 1911, with hemiplegia (left side). On September 5 she lost control of left hand, arm, and leg; fell to the floor but was at no time unconscious and retained the power of speech. When admitted the patient's face seemed unaffected; the tongue protruded in the median line. There was no paralysis of the palate. Complete loss of power and marked loss of tone in arm and leg were noted. The biceps and triceps reflexes of the left arm were absent. The knee-jerk was absent. Babinski's sign was present on the left side. Sense of position was lost in the left arm and leg. The sense of heat and cold was intact in the left arm and left leg above a level 4 cm. below the knee. Pain sense was lost in the left arm below the shoulder and in the left leg below the knee. Some loss of pain sensibility was found between the left knee and the hip.

The blood flow in the hands was examined April 16, 1912. At this time there had been noticeable improvement in the left leg, but not in the arm or hand. The hands were in bath at 3:21 p. m., in calorimeters at 3:32, out of calorimeters at 3:52. Mouth temperature 37.45 C. Pulse 104. The left hand as it hung down in the water pained her somewhat and therefore the vasomotor reaction was not tested.

TABLE 12.—Calorimetric Measurements in Case of Mrs. Eva M.

Time	Right	Left	Room	Time	Right	Left	Room
3:33	30.53	30.41	23.7	3:44	30.76	30.58	
3:34	30.50	30.43		3:45	30.79	30.60	23.3
3:35	30.55	30.46		3:46	30.81	30.61	
3:36	30.59	30.48		3:47	30.845	30.63	
3:37	30.62	30.50		3:48	30.88	30.645	
3:38	30.635	30.52	22.7	3:49	30.90	30.66	
3:39	30.65	30.525		3:50	30.93	30.68	
3:40	30.67	30.53		3:51	30.95	30.70	
3:41	30.69	30.535		3:52	30.99	30.73	
3:42	30.70	30.54		4:02	30.88	30.63	
3:43	30.72	30.555					

Cooling of calorimeters in ten minutes, R., 0.11 C., L., 0.10 C. Volume of right hand 334 c.c., of left hand 328 c.c. Water equivalent of calorimeters with contents, R., 3,362, L., 3,357.

The flow in the right hand in Mrs. Eva M. was 6.30 grams and in the paralyzed left hand 4.38 grams per 100 c.c. per minute with average room temperature 23 C.

George H., a man aged about 40 years, with typical motor aphasia and paralysis of the right arm and leg of 4 years' standing, had a blood flow of 7.26 grams per 100 c.c. per minute in the right hand and 9.82 grams in the left hand with room temperature 26.5 C. The ratio between the flows in the two hands was 1:1.35. During immersion of the left hand in cold water the flow in the right hand sank to 5.04 grams for the first three minutes and then increased to 7.93 grams per

7. Heart, 1911, iii, 81.

100 c.c. per minute for the next seven minutes. Immersion of the left hand in warm water coincided with a further and persistent diminution of the flow in the right to 5.74 grams. It is possible that the vasoconstriction was merely that not infrequently seen at the close of an experiment and does not represent an abnormally great prolongation of the initial vasoconstriction produced by the application of warmth to the contralateral hand. But the duration of the experiment was by no means great and it is at the end of long experiments that spontaneous and long-lasting diminution in the flow is apt to be witnessed. It seems more probable that there is an abnormal tendency to vasoconstriction in the paralyzed hand.

A week later, the flow was again measured in George H. and came out 9.38 grams for the right hand, and 13.21 grams for the left with room temperature 25.5 C. The ratio between the flows was 1:1.40, practically the same as at the previous examination. This indicates that the increase in the flow was due mainly at least to increased action of the heart and it is rather curious that the ratio of the pulse frequencies (1:1.26) agrees almost exactly with the ratio of the blood flows in the paralyzed hand at the two examinations (1:1.29). If the hand flows in this patient can be taken as an index of the heart output, which is justifiable at any rate so far as the absence of anemia is concerned,[8] this result would support the conclusion of Yandell Henderson[9] that with slow heart rates the minute output is proportional to the pulse frequency. There is no reason for thinking that the increased hand flows are due to a vasodilatation affecting the two hands in exactly the same proportion. In any case the external temperature could not be responsible for such an increase as it was about a degree lower at the second examination.

The flow in the feet of George H. was also examined on July 25, and came out 1.63 grams per 100 c.c. per minute for the right foot and 1.77 grams for the left. These flows in proportion to the hand flows are considerably below the normal.

George H. was admitted to the City Hospital, Oct. 5, 1909, with motor aphasia and paralysis of right arm and leg. He became paralyzed in 1908. When admitted he was unable to protrude the tongue. The right side of chest was markedly smaller than the left. There was a slight increase in the deep reflexes in the right arm and leg. The spinal fluid, 40 drops to minute, was clear, with 2 to 4 white cells to the c.c. and no Noguchi reaction. The blood flow in the hands was examined on July 18, and in the hands and feet on July 25, 1912. At this time aphasia is still complete. He seems to understand everything, but can only express assent or dissent by gestures. He can lift his arm to some extent but cannot move his left hand. He walks with a crutch and can stand by holding the back of a chair slightly. He can protrude the tongue easily in the median line and he can write. The knee-jerk is stronger on the

8. Jour. Exper. Med., 1913, xviii, 113.
9. Am. Jour. Physiol., 1913, xxxi, 288.

right side than on the left. Ankle clonus is present on the right but not on the left side. There is no defect of sensation. Some external squint of right eye and diplopia is present. No ptosis exists.

Blood flow examination of George H., July 18, 1912: Hands were in bath at 2:04 p. m., in calorimeters at 2:15. Some minutes elapsed before the right hand was got properly into the calorimeter. At 2:31 p. m. left hand was put into water at 8 C. Pulse 68. At 2:41 left hand was put into water at 43 C. At 2:51 right hand was removed from calorimeter.

TABLE 13.—Calorimetric Measurements in Case of George H.

Time	Right	Left	Room
2:14	31.52	31.45	26.5
2:19	31.54	31.64	
2:20	31.58	31.68	26.6
2:21	31.61	31.75	
2:22	31.64	31.79	
2:23	31.69	31.87	26.8
2:24	31.72	31.93	
2:25	31.76	31.98	
2:26	31.79	32.045	
2:27	31.825	32.08	26.7
2:28	31.87	32.14	
2:29	31.90	32.175	
2:30	31.935	32.24	
2:31	31.98	32.28	
2:32	32.005		
2:33	32.025	.....	26.7
2:34	32.04		
2:35	32.10		
2:36	32.135		
2:37	32.18		
2:38	32.22	.....	26.4
2:39	32.25		
2:40	32.28		
2:41	32.295		
2:42	32.31		
2:43	32.33	.....	26.4
2:44	32.365		
2:45	32.38		
2:46	32.395	.....	26.4
2:47	32.42		
2:48	32.45		
2:49	32.475		
2:50	32.50		
2:51	32.52		
3:18	32.25	31.87	

Cooling of calorimeters, R., 0.27 C. in twenty-seven minutes, L., 0.41 C. in forty-seven minutes. Volume of right hand 464 c.c., of left hand 500 c.c. Mouth temperature 36.95 C. Blood pressure left arm, systolic 90, 82 (sound gone). Another observation 92, 85.

Blood flow examination of George H., July 25, 1912: Results on the flow in the feet are given in the general table.

The hands were in bath at 2:46½ p. m., in calorimeters at 2:56, out of calorimeters at 3:09.

TABLE 14.—Calorimetric Measurements in Case of George H.

Time	Right	Left	Room
2:54	31.38	31.36	25.2
2:57	31.38	31.39	
2:58	31.43	31.47	25.4
2:59	31.49	31.58	
3:00	31.53	31.65	25.7
3:01	31.59	31.73	
3:02	31.66	31.795	25.5
3:03	31.72	31.865	
3:04	31.75	31.945	25.55
3:05	31.80	32.00	
3:06	31.85	32.075	25.7
3:07	31.89	32.165	
3:08	31.91	32.23	25.7
3:09	31.92	32.27	
3:17	31.82	32.17	

Cooling of calorimeters in eight minutes, 0.10 C. for R. and L. Volume of right hand 455 c.c., of left 497 c.c. Water equivalent of hand calorimeters and contents, R., 3,459, L., 3,492. Rectal temperature 37.4 C.

Dennis H., a structural iron worker, aged 41, was admitted to the City Hospital, June 19, 1911, with hemiplegia of the left side. Walking along the street on July 15, he fell unconscious and remained so about fifteen minutes. He had been a hard drinker; had gonorrhea and probably lues. No anemia was present (hemoglobin 100 per cent.). The tongue protruded in the median line. The head was held toward the right rather than the left. He was unable to move the left arm and leg. The patellar, Achilles, biceps and triceps reflexes on the left side were exaggerated. No Babinski sign or ankle clonus was

present. Epicritic and protopathic sensations over left leg were gone. Deep sensibility was present. Epicritic, protopathic, and deep sensibility was present in the arm but was greatly diminished. The same was true over the left side of the neck and face. No loss of power was seen in the face. Systolic blood pressure varied from 140 to 118 during the period of observation. On April 11, 1912, the blood flow in the hands was measured. At this time the left leg had recovered considerably, although he still used it very little. The left hand and arm were still quite powerless.

For the first six minutes in the calorimeters the flow in the right hand was 2.84 grams and in the left 1.80 grams per 100 c.c. per minute. During the immersion of the hands in the calorimeters the flow continued to increase gradually in both hands but particularly in the left so that for the whole period of immersion in the calorimeters (seventeen minutes) the flows came out 4.19 grams and 3.75 grams per 100 c.c. per minute for the right and left hands respectively. For the last six minutes of this period the flows were 4.92 grams for the right and 4.80 grams for the left hand. This gradual increase of the flow is observed under two conditions, first, when the flow is permanently small, and secondly, when an initial vasoconstriction is present, due either to nervousness on the part of the patient or to an abnormal sensitiveness of the vasomotor mechanism to the procedures necessarily involved in the measurement. In the case of Dennis H. both of these circumstances probably conspired. That a considerable tendency to vasoconstriction exists in the paralyzed hand was shown in the tests of the vasomotor reflexes. When the right hand was immersed in cold water the flow in the left was reduced from 4.80 grams to 3.49 grams per 100 c.c. per minute for the first seven minutes, to rise to 5.90 grams per 100 c.c. per minute for the remaining seven minutes of immersion of the right hand in the cold water. This constitutes a fair reflex vasoconstriction, particularly considering the small initial flow, and it endures, if anything, longer than normal. The moderate vasodilatation which succeeded was rather diminished than increased by subsequent immersion of the right hand in warm water.

TABES DORSALIS

In the five cases of tabes examined, the flow in both hands and feet was found subnormal, the deficiency being greater in the feet than in the hands. The vasomotor reflexes were quite feeble. The poor reflex response is especially striking when coupled with distinct or even acute perception of the sensations of cold and warmth, as in the case of Joseph S.

Joseph S., a laborer, aged 54, was admitted to the City Hospital, August 5, with tabes dorsalis. He had had pain and "funny feelings" for five years in both legs. Says he cannot feel over the hands or feet, but feels pin pricks somewhat. He also complains of sphincter trouble, and has a history of gonorrhea and lues. The spinal fluid, 120 drops per minute, 200 cells per c.c., shows

a strongly positive Noguchi reaction. The pupils, pin point, react to accommodation. There is little if any reaction to light. The nasal septum is perforated. Heart examination is negative. There is marked arteriosclerosis. Knee-jerk, Achilles and cremasteric reflexes are absent. Romberg sign is marked. Muscular incoordination is shown.

The blood flow in the hands and feet was measured August 7. Pulse 124. Hands in bath at 1:46½ p. m., in calorimeters at 1:57¾ p. m. At 2:12 left hand immersed in water at 8.4 C. He feels that the water is cold and soon begins to complain of it, withdrawing the hand momentarily. At 2:24 left hand put into water at 42.8 C. At 2:35 right hand removed from calorimeter.

TABLE 15.—Calorimetric Measurements in Case of Joseph S.

Time	Right	Left	Room
1:57	31.20	31.13	
1:59	31.22	31.15	24.9
2:00	31.26	31.18	
2:01	31.295	31.20	25.1
2:02	31.325	31.22	
2:03	31.365	31.255	
2:04	31.40	31.27	25.0
2:05	31.43	31.295	
2:06	31.46	31.315	
2:07	31.495	31.35	25.1
2:08	31.52	31.365	
2:09	31.56	31.38	
2:10	31.58	31.405	25.1
2:11	31.605	31.43	
2:12	31.63	31.45	
2:13	31.67	.....	25.0
2:14	31.695		
2:15	31.705		
2:16	31.73		
2:17	31.76		
2:18	31.785	.....	25.0
2:19	31.81		
2:20	31.83		
2:21	31.865		
2:22	31.895		
2:23	31.91		
2:24	31.935		
2:25	31.96	.....	25.0
2:26	31.985		
2:27	32.00		
2:28	32.025	.....	25.15
2:29	32.05		
2:30	32.08		
2:31	32.09		
2:32	32.11		
2:33	32.13	.....	25.4
2:34	32.16		
2:35	32.19		
2:45	32.075	31.13	

Cooling of calorimeters, R., 0.115 C. in ten minutes, L., 0.32 C. in thirty-three minutes. Volume of right hand in calorimeter 425 c.c., of left hand 441 c.c. He is right handed, but from the way in which he held his hand, a somewhat smaller proportion of the right hand was in the calorimeter than of the left. This is taken account of in the volume measurement.

The flow in the right foot in this patient was 0.76 gram and in the left foot 0.88 gram per 100 c.c. per minute with the relatively high room temperature 25 C. The flow in the right hand was 5.86 grams and in the left 4.33 grams with the same room temperature. Probably the inequality in the flows in the two hands is not so great as it appears to be. For, as has been mentioned in the protocol, the right hand was not inserted so deeply into the calorimeter as the left, and it has been shown that the flow per unit of volume is greater in the distal than in the proximal portions of the hand, corresponding with the relatively greater surface. However, in our study of diseases of the nervous system there have been numerous instances of the existence of inequalities of flow in the two hands or feet which could not be connected with any known cause. It may indeed be said that such inequalities are common features of those diseases. It has been suggested that vasomotor conditions, probably essentially connected with the pathology

or pathologic physiology of the morbid state, are responsible for these inequalities.[10]

On immersion of the left hand (of Joseph S.) in cold water, which apparently caused him considerable discomfort, the flow in the right was but slightly changed, falling to 5.21 grams per 100 c.c. per minute for the first four minutes and then rising slightly again to 5.43 grams per 100 c.c. per minute for the remaining eight minutes of the immersion. This is truly an insignificant vasoconstrictor reaction. Immersion of the left hand in warm water caused a slight diminution of the flow in the right, to 5.22 grams per 100 c.c. per minute for the first five minutes, which then gave place to a correspondingly slight increase (to 5.48 grams for the next six minutes). Such slight reflex vasomotor effects have certainly rarely been observed in other conditions. It must be noted, however, that decided arteriosclerosis was present in this man and this condition is itself associated with relatively small vasomotor reflexes.[11]

In a case of tabes examined at the dispensary (Abe K.) the hand flows were only 1.27 grams for the right and 1.22 grams for the left, with room temperature 23 C. Probably the circulatory condition noted in the protocol was a factor in the small flow, as there was evidence of some loss of cardiac compensation (cyanosis, edema of legs and feet).

Abe K., a waiter, aged 59, was admitted to the dispensary January 30. Six weeks ago he began to lose his sight and is now almost blind. For two months he has been unsteady on his feet, especially in walking at night. Some exophthalmos is noted. Slight ptosis of both eyes exists. The face and lips are cyanotic. The pupils are irregular, fixed, unequal, with no reaction to light or accommodation. His gait is uncertain, with left foot flapped. The knee-jerk is much diminished. The Achilles reflex is absent. There is no Babinski sign. Edema of feet and legs is present, with hypotonus of muscles. Sensibility to touch, pain, heat and cold is diminished below the knees. The muscle sense is not good. There is incoordination of the hands. There is a slight Romberg sign. Examination of lungs is negative. The heart dulness extends 2 cm. to the left of the nipple line. There is also increase of dulness to the right of the sternum. The aortic second sound is much accentuated. The edge of the liver is palpable 3 finger breadths below the costal margin on deep inspiration. The blood flow in the hands was measured on February 1.

W. B. C., a cigarmaker, aged 57, was admitted to Lakeside Hospital, November 8, with tabes dorsalis. He complains of difficulty in walking and ataxia, most marked in left leg. There are no sensory disturbances, except that he does not feel hot water on his feet unless it is pretty hot. Up to the present illness his eyesight has been good. There is external strabismus of the right eye. The pupils are unequal and irregular and do not react to light, but react to accommodation. Knee-jerk is absent. The hands are ataxic; he has difficulty in buttoning his clothes. Examination of heart and lungs is negative. The blood flow was examined November 11.

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10. Paper XII of this series.

11. Stewart, G. N.: The Blood Flow in the Hands and Feet in Certain Diseased Conditions of the Vessels or of Their Nervous Mechanism, The Archives Int. Med., 1914, xiii, 177.

The feet were in bath at 2:23 p. m., in calorimeters at 2:36. At 3:07 the left foot was put into water at 44.3 C. He feels it comfortably warm. At 3:19 right foot was taken out of calorimeter. Pulse 84.

TABLE 16.—CALORIMETRIC MEASUREMENTS IN CASE OF W. B. C.

Time	Right	Left	Room
2:34	31.33	31.26	20.9
2:37	31.23	31.18	20.9
2:39	31.22	31.17	20.9
2:41	31.19	31.155	
2:43	31.17	31.135	20.9
2:45	31.14	31.13	21.2
2:47	31.11	31.10	21.3
2:49	31.09	31.085	21.3
2:51	31.065	31.07	21.35
2:53	31.04	31.06	21.4
2:55	31.03	31.055	21.7
2:57	31.01	31.05	21.8
2:59	30.99	31.04	21.8
3:01	30.97	31.03	22.0
3:03	30.95	31.01	22.0
3:05	30.925	30.99	21.9
3:07	30.90	30.98	
3:09	30.89	.....	21.9
3:11	30.88	.....	21.8
3:13	30.865	.....	21.7
3:15	30.84	.....	21.7
3:17	30.825		
3:19	30.81	.....	21.9
3:21	30.74	30.68	
3:34	30.52	30.47	

Cooling of foot calorimeters in thrirteen minutes, R., 0.22 C., L., 0.21 C. Volume of right foot 925 c.c., of left foot 943 c.c. Water equivalent of feet calorimeters with contents, R., 3,660, L., 3,673.

The hands were in bath at 3:40 p. m., in calorimeters at 3:48¾. At 4:06 the left hand was put into water at 44.7 C. He feels it warm. At 4:20 left hand was put into water at 13 C. He feels it rather cold. Right hand taken out of calorimeter at 4:29 p. m.

TABLE 17.—CALORIMETRIC MEASUREMENTS IN CASE OF W. B. C.

Time	Right	Left	Room
3:48	31.75	31.76	
3:50	31.74	31.75	23.3
3:51	31.73	31.74	23.2
3:52	31.73	31.74	
3:53	31.74	31.75	23.2
3:54	31.74	31.75	23.2
3:55	31.75	31.75	
3:56	31.76	31.755	23.1
3:57	31.77	31.765	
3:58	31.78	31.775	
3:59	31.79	31.785	23.0
4:00	31.80	31.80	
4:01	31.81	31.82	22.9
4:02	31.82	31.83	
4:03	31.835	31.84	22.9
4:04	31.85	31.85	
4:05	31.86	31.86	23.0
4:06	31.87	31.86	
4:07	31.88		
4:08	31.89	.....	23.0
4:09	31.89		
4:10	31.89	.....	22.9
4:11	31.89		
4:12	31.90	.....	22.7
4:13	31.90		
4:14	31.91	.....	22.8
4:15	31.93		
4:16	31.95	.....	22.9
4:17	31.97		
4:18	31.99	.....	22.9
4:19	31.99		
4:20	32.01		
4:21	32.01	.....	22.8
4:22	32.02		
4:23	32.03	.....	22.5
4:24	32.04		
4:25	32.05	.....	22.7
4:26	32.06		
4:27	32.065	.....	22.5
4:28	32.07		
4:29	32.08	.....	22.7
4:38	31.95	31.44	

Cooling of hand calorimeters, R., 0.13 C. in nine minutes, L., 0.42 C. in thirty-two minutes. Volume of right hand 380 c.c., of left 388 c.c. Water equivalent of hand calorimeters with contents, R., 3,399, L., 3,405. Rectal temperature 36.90 C.

In W. B. C. the blood flow in the right foot was 0.54 gram and in the left foot 0.87 gram per 100 c.c. per minute with room temperature 21.5 C. During immersion of the left foot (for a period of twelve minutes) in warm water, the flow in the right was 0.75 gram per 100 c.c. per minute. The hand flows before testing the vasomotor reaction

were 5.42 grams for the right, and 5.05 grams for the left with room temperature 22.9 C. Immersion of the left hand in warm water reduced the flow in the right (for the first five minutes) to 4.01 grams per 100 c.c. per minute. For the remaining nine minutes of the period of immersion, the flow in the right hand rose to 6.16 grams per 100 c.c. per minute. A subsequent immersion of the left hand in cold water caused a diminution in the flow in the right to 3.26 grams but only for a single minute, the flow then rising for the remainder of the period of immersion to 5.3 grams per 100 c.c. per minute.

Gabriel M., a barber, aged 41, was admitted to Lakeside Hospital, November 13, with the diagnosis of tabes. He complains of seeing double, that the left leg is weaker than the right and that he gets tired in walking. The patellar and Achilles reflexes are absent from both sides. The biceps and triceps reflexes are present in both arms. The plantar reflex is normal. There is marked hypotonus of the iliofemoral muscles with ataxia. There is ataxia also of the toes. Vibration is everywhere perceived. Hypesthesia to the needle is noted in both lower extremities, with great delay in transmission. Over the left leg the delay is fully two seconds. Romberg's sign is positive. The spinal fluid is clear under normal pressure, the cell count 8, Noguchi negative, Wassermann strongly positive. The grip of the hands is fairly strong. There is no incoordination of the hand movements. Sometimes a good deal of pain is present in the legs especially at night. The feet are habitually cold. Particulars of the first examination of the blood flow in the hands on November 17 are given in the general table.

Second examination of blood flow in Gabriel M., November 19: Hands in bath at 3:43 p. m., in the calorimeters at 3:52. At 4:10 p. m. the left hand was put into water at 43 C. At 4:20 p. m. the right hand was taken out of the calorimeter. Pulse 100.

TABLE 18.—Calorimetric Measurements in Second Examination of Gabriel M.

Time	Right	Left	Room
3:51	31.73	31.64	
3:53	31.72	31.63	24.0
3:54	31.715	31.625	24.0
3:55	31.71	31.62	
3:56	31.71	31.62	24.0
3:57	31.705	31.61	
3:58	31.71	31.62	24.1
3:59	31.715	31.63	
4:00	31.72	31.635	24.1
4:01	31.72	31.63	
4:02	31.72	31.63	24.1
4:03	31.725	31.635	
4:04	31.73	31.64	
4:05	31.735	31.645	24.2
4:06	31.74	31.65	
4:07	31.75	31.65	24.15
4:08	31.755	31.655	
4:09	31.76	31.66	24.2
4:10	31.765	31.66	
4:11	31.77		
4:12	31.77	.....	24.2
4:13	31.78		
4:14	31.78	.....	24.2
4:15	31.79		
4:16	31.795	.....	24.3
4:17	31.795		
4:18	31.795	.....	24.4
4:19	31.80	.....	24.3
4:20	31.81		
4:33	31.65		

Cooling of hand calorimeters, R., 0.16 C. in thirteen minutes, L., 0.29 C. in twenty-three minutes. Volume of right hand, 424 c.c., of left 407 c.c. Water equivalent of calorimeters with contents, R., 3,434, L., 3,420. Rectal temperature 37.20 C.

Third examination of blood flow in Gabriel M., November 24. Feet in bath at 2:45 p. m., in calorimeters at 2:56. At 3:44 right foot put into water at 43 C. At 3:58 right foot put into water at 8.7 C. He felt it very cold at first. At 4:12 p. m. left foot taken out of calorimeter.

TABLE 19.—Calorimetric Measurements in Third Examination of Gabriel M.

Time	Right	Left	Room
2:55	31.82	31.86	20.1
2:58	31.63	31.66	
3:00	31.54	31.57	
3:02	31.47	31.52	20.3
3:04	31.39	31.45	20.7
3:06	31.32	31.39	20.8
3:08	31.26	31.35	21.0
3:10	31.21	31.29	21.0
3:12	31.17	31.25	21.1
3:14	31.12	31.20	21.2
3:16	31.08	31.16	21.3
3:18	31.05	31.13	21.4
3:20	31.01	31.10	21.5
3:22	30.98	31.07	21.7
3:24	30.96	31.05	21.7
3:26	30.94	31.03	21.9
3:28	30.92	31.01	22.0
3:30	30.90	30.985	
3:32	30.895	30.97	22.1
3:34	30.89	30.955	22.2
3:36	30.88	30.95	22.2
3:38	30.88	30.94	22.3
3:40	30.87	30.93	
3:42	30.87	30.92	
3:44	30.86	30.90	
3:46	30.795	30.885	22.4
3:48	.....	30.87	22.5
3:50	.....	30.865	22.6
3:52	.....	30.86	22.6
3:54	.....	30.855	22.6
3:56	.....	30.85	22.7
3:58	.....	30.845	
4:00	.....	30.835	22.8
4:02	.....	30.83	22.8
4:04	.....	30.82	
4:06	.....	30.81	22.9
4:08	.....	30.80	23.1
4:10	.....	30.79	22.9
4:12	.....	30.77	
4:13	.....	30.755	
4:27	30.09	30.52	

Cooling of foot calorimeters, R., 0.705 C. in forty-one minutes, L., 0.235 C. in fourteen minutes. Volume of right foot 1,092 c.c., of left 1,087 c.c. Water equivalent of foot calorimeters with contents R., 3,783, L., 3,779. Pulse 108.

Hands in bath at 4.33½ p. m., in calorimeters at 4:32, out of calorimeters at 4:43.

TABLE 20.—Calorimetric Measurements in Third Examination of Gabriel M.

Time	Right	Left	Room
4:31	31.48	31.39	24.2
4:33	31.42	31.36	24.7
4:34	31.42	31.36	24.5
4:35	31.415	31.355	24.2
4:36	31.42	31.36	
4:37	31.42	31.36	23.7
4:38	31.41	31.36	23.4
4:39	31.41	31.355	
4:40	31.41	31.255	23.4
4:41	31.41	31.365	
4:42	31.41	31.365	
4:43	31.42	31.37	23.9
4:49	31.32	31.28	

Cooling of hand calorimeters in six minutes, R., 0.10 C., L., 0.09 C. Rectal temperature 37.55 C. Volume of right hand 425 c.c., of left 390 c.c. Water equivalent of hand calorimeters with contents, R., 3,435, L., 3,407.

The flow in the right hand of Gabriel M. at the first examination was 1.0 gram, in the left 1.37 grams per 100 c.c. per minute with room temperature 22.6 C. Two days later the flows were 2.91 grams and 2.86 grams for the right and left hands respectively with the higher room temperature of 23.9 C. Immersion of the left hand in warm water caused scarcely any increase of flow in the right hand, which came out 3.07 grams per 100 c.c. per minute during the ten minutes of the period of immersion. The flow in the right foot at the same examination was 0.56 gram, and in the left 0.62 gram. The ratio of the combined foot flows to the combined hand flows was 1:4.89, indicating a relatively greater deficiency in the feet than in the hands. This is characteristic of all the cases of tabes examined. For a period

of twenty-two minutes immersion of the right foot in warm water the flow in the left foot was slightly increased (to 0.89 gram per 100 c.c. per minute).

At the third examination the flow in the right hand of Gabriel M. was 2.77 grams and in the left hand 2.88 grams with room temperature 22.1 C. The flow in the right foot before testing of the vasomotor reflexes was 0.96 gram and in the left foot 0.73 gram. The ratio of the combined foot to the combined hand flows was 1:3.93. During immersion of the right foot in warm water the flow in the left foot (for the first four minutes of the immersion) sank to 0.65 gram, and then rose to 0.92 gram per 100 c.c. per minute for the remaining ten minutes of the immersion period. When the right foot was subsequently put into cold water the change was slight, the flow in the left foot being 0.84 gram per 100 c.c. per minute for the first four minutes of the immersion and 0.70 gram for the remaining ten minutes.

TABLE 21.—Calorimetric Measurements in Second Examination of John M.

Time	Right	Left	Room
2:14	31.79	31.68	
2:15	31.77	31.67	
2:16	31.78	31.68	23.8
2:17	31.785	31.69	
2:18	31.795	31.70	
2:19	31.82	31.73	24.4
2:20	31.85	31.76	24.2
2:21	31.88	31.79	
2:22	31.90	31.82	
2:23	31.92	31.85	
2:24	31.94	31.87	23.9
2:25	31.98	31.90	
2:26	32.00	31.93	
2:27	32.025	.....	24.1
2:28	32.05		
2:29	32.07	.....	24.2
2:30	32.09		

Time	Right	Left	Room
2:31	32.115	.....	24.4
2:32	32.15		
2:33	32.185	.....	24.7
2:34	32.21		
2:35	32.24		
2:36	32.28		
2:37	32.31	.....	24.8
2:38	32.335		
2:39	32.37	.....	24.5
2:40	32.395		
2:41	32.42	.....	24.0
2:42	32.45		
2:43	32.49	.....	23.4
2:44	32.52	.....	23.4
2:45	32.57	.....	23.8
2:52	32.47	31.55	

Cooling of hand calorimeters, R., 0.10 C. in seven minutes, L., 0.38 C. in twenty-six minutes. Volume of right hand 426 c.c., of left 399 c.c. Water equivalent of hand calorimeters with contents, R., 3,436, L., 3,414. Pulse 96.

John M., a laborer, aged 45, was admitted December 2 at Lakeside Hospital with the diagnosis of tabes, complaining of incontinence of urine and trouble in walking. A history was given of gonorrhea. He says he was bit in the arm twenty-eight years ago by a person supposed to have had lues. He denies having had chancre. His present illness seems to have commenced fourteen years ago. The reflexes are hypo-active in the biceps and supinator of both arms. The lower extremities are ataxic. The patellar and ankle reflexes are absent, also the plantar reflexes. There is no Babinski or Kernig's sign. Romberg's sign is positive. He feels a point on the feet but the response is slow. He walks fairly well, better than some time ago, he says. The pupils are equal, central and regular, but do not react to light and very sluggishly to accommodation. The skin of the nose is covered entirely by scar tissue; the septum is deficient posteriorly. Blood examination, erythrocytes 4,976,000, white blood corpuscles 6,200, hemoglobin 80 per cent. The blood flow was examined on

December 3 and December 8. The particulars of the flow in the feet at first examination of John M. are given in the general table.

Second examination of blood flow in John M., Dec. 8, 1914. Hands were in bath at 2:05 p. m., in calorimeters at 2:14½. At 2:26 p. m. the left hand was put into water at 8 C. At 2:36 p. m. the left hand was put into water at 43.1 C. At 2:45 p. m. the right hand was taken out of the calorimeter.

The feet were in bath at 2:55 p. m., in calorimeters at 3:06. At 3:41 p. m. right foot was put into water at 8.3 C. He feels it pretty cold. At 3:55 p. m. left foot taken out of calorimeter.

TABLE 22.—Calorimetric Measurements in Second Examination of John M. (Feet)

Time	Right	Left	Room
3:05	32.28	32.33	24.8
3:08	32.18	32.25	24.8
3:09	32.15	32.20	24.9
3:11	32.12	32.17	
3:13	32.11	32.16	24.5
3:15	32.10	32.155	
3:17	32.09	32.145	24.8
3:19	32.07	32.13	24.9
3:21	32.05	32.11	24.7
3:23	32.02	32.085	
3:25	32.00	32.07	24.5
3:27	32.00	32.065	
3:29	31.99	32.06	24.5
3:31	31.985	32.06	24.7
3:33	31.98	32.055	24.8
3:35	31.98	32.055	24.8
3:37	31.97	32.06	24.8
3:39	31.97	32.06	
3:41	31.96	32.065	24.8
3:43	31.88	32.065	24.7
3:45	.....	32.06	24.8
3:47	.....	32.055	
3:49	.....	32.05	24.5
3:51	.....	32.045	24.6
3:53	.....	32.04	24.8
3:55	.....	32.04	
3:58	.....	31.97	
4:04	31.51	31.86	

Cooling of foot calorimeters, R., 0.37 C. in twenty-one minutes, L., 0.11 C. in six minutes. Rectal temperature, 37.65 C. Volume of right foot, 1,006 c.c., of left, 1,001 c.c. Water equivalent of foot calorimeters with contents, R., 3,720, L., 3,716.

In John M. at the first examination the flows in the right and left foot respectively, before the vasomotor reflexes were tested, were 1.27 grams and 1.28 grams per 100 c.c. per minute, with room temperature 24.2 C. For a period of twelve minutes immersion of the right foot in cold water, the flow in the left was reduced to 0.95 gram per 100 c.c. per minute. Subsequent immersion of the right foot in warm water for a period of fourteen minutes caused an increase of the flow in the left to 1.52 grams per 100 c.c. per minute. Five days later the flow in the right hand was found to be 6.60 grams and in the left 7.57 grams with room temperature 24 C. When the left hand was put into cold water the flow in the right fell to 6.46 grams per 100 c.c. per minute for the first five minutes and then rose for the remaining five minutes of the period of immersion of the left hand, to 8.47 grams per 100 c.c. per minute, an insignificant reaction. When the left hand was subsequently immersed in warm water the flow in the right hand was only increased to 8.79 grams per 100 c.c. per minute for the whole nine minutes of the period of immersion. At the same examination the flow in the right foot came out, before the vasomotor reflexes were tested, 1.35 grams per 100 c.c. per minute and that in the left foot 1.57 grams, with room temperature 24.7 C. The ratio of the combined foot flow to the combined hand flow was 1:4.85. The room was warm and the

patient perspiring, so that the flows both in hands and feet are really more deficient than the actual numbers would suggest, and the same is true for the foot flows at the first examination. When the right foot was immersed in cold water the flow in the left foot was only slightly changed, falling to 1.39 grams per 100 c.c. per minute for the whole fourteen minutes of the immersion.

The case of Joseph K. is of interest, inasmuch as the suggested diagnosis of malingering was not, as regards the symptoms described in the legs, supported by the blood flow examination, which, on the contrary, indicated a real pathologic condition.

Joseph K., a laborer, aged 48, was admitted to the hospital June 17. There appears to be delayed sensation in the extremities. He says that he does not feel heat or vibratory sensation in the thighs. Pin pricks are apparently not well recognized. Knee-jerk and Achilles reflex are strong. He complains of pain in the left leg. Says he has cold sweats on legs and feet at night in bed. His legs feel cold to his hand, although he expects them to be warm since they are covered with sweat. He pinches his calf and says he feels nothing there. A zone on the calves is apparently anesthetic to contact. In front on the shins

TABLE 23.—Calorimetric Measurements in Case of Joseph K.

Time	Right	Left	Room	Time	Right	Left	Room
1:53	31.13	31.12		2:12	31.905		
1:55	31.12	31.125	27.2	2:13	31.925	.....	27.4
1:56	31.16	31.16		2:14	31.96		
1:57	31.21	31.22		2:15	31.995		
1:58	31.26	31.27	27.2	2:16	32.025	.....	27.4
1:59	31.31	31.325		2:17	32.05		
2:00	31.36	31.36		2:18	32.08		
2:01	31.42	31.41	27.3	2:19	32.12	.....	27.5
2:02	31.49	31.47		2:20	32.165		
2:03	31.54	31.525		2:21	32.205		
2:04	31.605	31.585	27.3	2:22	32.26		
2:05	31.68	31.64		2:23	32.30	.....	27.55
2:06	31.73	31.60		2:24	32.365		
2:07	31.76			2:25	32.42		
2:08	31.79	.....	27.3	2:26	32.48	.....	27.55
2:09	31.80			2:27	32.545		
2:10	31.825			2:33	32.49	31.505	
2:11	31.87						

Cooling of calorimeters, R., 0.055 C. in six minutes, L., 0.195 C. in twenty-seven minutes. Volume of right hand 495 c.c., of left hand 479 c.c. Water equivalent of calorimeters with contents, R., 3,491, L., 3,478. Rectal temperature 37.55 C.

at this level he feels contact, as also on the patellae and on the feet. He feels warm water on the feet. He says his hand "shortens" when he tries to write. His pupils react to light and accommodation. The chest examination reveals nothing special. Temperature normal. Blood examination on June 24 gave erythrocytes 5,120,000; leukocytes 9,400; hemoglobin 85 per cent. Two Wassermann tests were negative for blood, as also the Wassermann and Noguchi reactions for spinal fluid. On June 26 pin pricks were better appreciated over the thighs; the knee-jerks were not strong, but were equal on the two sides. The patient was discharged on July 3 "cured," with a suggestion that he was malingering. Blood flow in the hands and feet was examined on June 26. The day was warm.

Hands in bath at 1:41 p. m., in calorimeters at 1:54⅓ p. m. At 2:06 p. m. left hand immersed in cold water (8.5 C.). He says he feels the water very

cold. At 2:16 p. m. left hand put into water at 41.4 C. At 2:27 the right hand taken out of calorimeter.

The flow in the right hand in Joseph K. was 8.94 grams and in the left 8.75 grams per 100 c.c. per minute with room temperature 27.3 C. For the man's age and the high room temperature, these flows are fair but by no means large, and the slight preponderance in the right hand is entirely normal. The vasomotor reflexes in the hand both to cold and warmth were also normal in intensity and duration. In the feet, on the contrary, the flows came out extremely small, especially taking into account the high room temperature (0.50 grams for the right and 0.54 gram per 100 c.c. per minute for the left foot, with room temperature 26.4 C.). This is quite in agreement with the patient's statement as to the coldness of his feet. Also there was total absence of any vasomotor reflex in the left foot when the right was immersed for ten minutes in warm water, the flow remaining unchanged (0.53 gram). While the patient might have showed some temporary improvement in his not very obtrusive symptoms during his stay in the hospital, it seems unlikely that such definite blood flow results for the feet should be devoid of significance. They at any rate would suggest the necessity in such a case of renewed careful examination of the patient before the suggestion of malingering could be accepted.

In Fred L., a man aged 22, with a glioma of the occipital lobe, the striking feature of the blood-flow examination was the great intensity of the contralateral vasomotor reflexes both to heat and cold. Two examinations were made within eight days and this was clearly seen at both. It is a plausible suggestion that the increased intracranial pressure, of which there were evident symptoms, may have rendered the vasomotor centers hyperexcitable. It is possible also that the rather small flows for the age of the patient might have been due to a peripheral vasoconstriction produced in this way in the interest of the brain circulation.

Fred. L. was first admitted to Lakeside Hospital, June 30, 1908. He complained of dizzy attacks and severe headache. The attacks occurred about once a week and varied in intensity. There was never any nausea or vomiting. Severe headaches had occurred nearly every day since his first trouble. Examination of the eyes showed choked disk and hemianopsia. He could not see objects at his right. Hearing, the same on both sides, was a little less acute than normal. Numerous lumbar punctures were made, and finally a decompression operation was done. Two years later he reported to the dispensary much improved. He again reported July 18, 1911, that occipital headache came on at night and prevented sleep. Only large doses of morphin quieted him at all. He was readmitted to the hospital, Oct. 8, 1912. Hemianopsia was present as before. The blood flow in the hands was twice examined (Nov. 18 and Nov. 26, 1912). On November 27 he left the hospital for Thanksgiving and returned on November 28 with severe headache and vomiting. On November 29 an operation was resolved on, during which he died. The necropsy showed a

glioma with cystic degeneration in the left occipital lobe resting on the tentorium. The cyst measured about 5 cm. by 3 cm.

First blood flow examination of Fred. L.: Hands in bath at 3:07 p. m., in calorimeters at 3:20½. At 3:38 left hand immersed in water at 43 C. Pulse 88. At 3:50 p. m. the left hand was put into water at 11.2 C. He feels the water very cold. At 4:02 right hand was removed from calorimeter.

TABLE 24.—Calorimetric Measurements in Case of Fred. L.

Time	Right	Left	Room
3:20	30.44	30.42	
3:22	30.37	30.40	
3:23	30.38	30.41	
3:24	30.38	30.42	
3:25	30.385	30.43	22.0
3:26	30.41	30.47	
3:27	30.43	30.50	22.1
3:28	30.48	30.53	
3:29	30.52	30.565	22.1
3:30	30.58	30.58	
3:31	30.60	30.60	22.0
3:32	30.61	30.62	
3:33	30.63	30.64	22.0
3:34	30.66	30.68	
3:35	30.69	30.70	
3:36	30.71	30.71*	
3:37	30.71	30.71	
3:38	30.73	30.70	
3:39	30.74		
3:40	30.765		
3:41	30.80		
3:42	30.83		
3:43	30.88		
3:44	30.92		
3:45	30.96		
3:46	31.01		
3:47	31.06		
3:48	31.09	30.58	
3:49	31.12		
3:50	31.18		
3:51	31.18		
3:52	31.185		
3:53	31.19		
3:54	31.19	.....	23.0
3:55	31.19		
3:56	31.195	.....	22.8
3:57	31.225		
3:58	31.245	.....	22.5
3:59	31.25	.....	22.1
4:00	31.27		
4:01	31.28	.....	22.2
4:02	31.31		
4:12	31.19		

Cooling of calorimeters in ten minutes, R., 0.12 C., L., 0.11 C. Volume of right hand 385 c.c., of left 377 c.c. His hands are thin. Water equivalent of calorimeters with contents, R., 3,403, L., 3,397. Rectal temperature 37.7 C.

* He is paying great attention to the preparations for the warm water test.

TABLE 25.—Calorimetric Measurements in Second Examination of Fred. L.

Time	Right	Left	Room
10:57½	31.17	31.19	21.0
11:00	31.195	31.21	
11:01	31.205	31.225	
11:02	31.21	31.26	21.5
11:03	31.22	31.28	
11:04	31.24	31.295	21.5
11:05	31.295	31.31	
11:06	31.295	31.335	21.4
11:07	31.32	31.35	
11:08	31.34	31.37	21.35
11:09	31.39	31.395	
11:10	31.395	31.405	
11:11	31.42	31.42	
11:12	31.45	31.435	
11:13	31.50	31.46	
11:14	.....	31.465	20.9
11:15	.....	31.48	
11:16	.....	31.505	
11:17	.....	31.555	20.7
11:18	.....	31.605	
11:19	.....	31.635	20.7
11:20	.....	31.675	
11:21	.....	31.69	
11:22	.....	31.73	20.6
11:23	.....	31.76	
11:24	.....	31.785	20.6
11:25	.....	31.795	
11:26	.....	31.80	20.7
11:27	.....	31.795	
11:28	.....	31.80	
11:29	.....	31.805	20.7
11:30	.....	31.81	
11:31	.....	31.82	
11:32	.....	31.82	
11:33	.....	31.82	20.7
11:34	.....	31.815	
11:35	.....	31.825	
11:36	.....	31.835	
11:37	.....	31.86	20.7
11:38	.....	31.875	
11:39	.....	31.89	20.7
11:40	.....	31.90	
11:41	.....	31.915	
11:42	.....	31.935	
11:43	.....	31.95	20.7
11:44	.....	31.965	
11:45	.....	31.975	
11:46	.....	31.99	
12:02	30.82	31.725	

Cooling of calorimeters, R., 0.68 C. in 49 minutes, L., 0.265 C. in sixteen minutes. Volume of right hand 389 c.c., of left 380 c.c. Water equivalent of calorimeters with contents, R., 3,406, L., 3,399. Rectal temperature 37.75 C.

Second blood flow examination of Fred. L.: He says he is feeling better than at the previous examination though he was sick (vomiting) all yesterday morning. Hands were in bath at 10:45½ a. m., in calorimeters at 10:58½. At 11:13 a. m. the right hand was put into water at 43 C. At 11:24 a. m. the right hand was put into water at 10.5 C. At 11:35 right hand was again immersed in water at 43 C. At 11:46 right hand was taken out of calorimeter. Pulse 100.

At the first examination the flow in the right hand in Fred L. was 5.43 grams and in the left 4.80 grams per 100 c.c. per minute with room temperature 22 C. (ratio 1:1.13). Immersion of the left hand in warm water reduced the flow for the first two minutes in the right hand to 4.18 grams per 100 c.c. per minute. For the remaining ten minutes of the period of immersion the flow in the right hand rose to 8.28 grams per 100 c.c. per minute, a marked reflex vasodilatation. When the left hand was now immersed in cold water the flow in the right hand fell to 2.28 grams per 100 c.c. per minute for the first six minutes of the period of immersion. For the remaining six minutes of the period it rose somewhat but only to 4.84 grams. The reflex vaso-constriction was thus very intense and durable. At the second examination the flow for the right hand, before the vasomotor reaction was tested, was 6.15 grams per 100 c.c. per minute and for the left 5.49 grams with room temperature 21.4 C. (ratio 1:1.12, almost precisely the same as at the previous examination). The vasomotor reflex tests also showed intense and persistent effects.

In a young man (J. S.), recovering from tetanus after antitoxin treatment, vasomotor reflexes fully as intense were observed. There was no direct evidence that this condition was due to the action of the tetanus toxin or antitoxin on the nervous system, but the extent of the crossed vasomotor reflexes was certainly notable.

TABLE 26.—Calorimetric Measurements in Case of J. S.

Time	Right	Left	Room	Time	Right	Left	Room
1:37	30.53	30.54		1:54	30.74		
1:39	30.49	30.51	25.5	1:55	30.795		
1:40	30.48	30.49		1:56	30.83		
1:41	30.47	30.49		1:57	30.89		
1:42	30.48	30.50		1:58	30.935	.....	26.0
1:43	30.495	30.52		1:59	30.995		
1:44	30.51	30.54	26.0	2:00	31.05		
1:45	30.535	30.56		2:01	31.08		
1:46	30.58	30.61		2:02	31.095		
1:47	30.61	30.64		2:03	31.10	.....	26.0
1:48	30.63	30.67	25.9	2:04	31.16		
1:49	30.65	30.72		2:05	31.22		
1:50	30.68	30.74		2:06	31.27	.....	25.8
1:51	30.69			2:07	31.31		
1:52	30.705	.....	26.2	2:08	31.37		
1:53	30.72			2:17	31.29	30.55	

Cooling of calorimeters, R., 0.08 C. in nine minutes, L., 0.19 C. in twenty-seven minutes. Volume of right hand 389 c.c., of left hand 358 c.c.

J. S., a young laborer, was admitted to the City Hospital, March 18, suffering from tetanus. On March 9 his right thumb was injured by a machine. On March 16 pain and stiffness were present in the jaw. Three days later his back

was stiff and painful; attacks of cramp-like rigidity occurred. When admitted there was a spastic condition of legs, arms and hands, and some spasm of the jaw. He was treated with large doses of antitoxin. The blood flow in the hands was examined on April 5. The thumb had nearly healed. The knee-jerks were still exaggerated.

The hands were in bath at 1:28 p. m., in calorimeters at 1:38. At 1:50 p. m. the left hand was immersed in water at 43.5 C. At 2:00 p. m. the left hand was put into water at 7 C. At 2:08 p. m. the right hand was taken out of the calorimeter. Pulse 92, rather weak. Mouth temperature 37.3 C.

The initial flow in the hands of J. S. was subnormal for his age and the room temperature (5.32 grams per 100 c.c. per minute for the right hand and 6.3 grams for the left, with room temperature 25.9 C.). On immersion of the left hand in warm water the flow in the right fell to 3.32 grams per 100 c.c. per minute for the first four minutes and then rose to 9.09 grams for the remaining six minutes of the immersion. When the left hand was now put into cold water the flow in the right was cut down to 3.9 grams per 100 c.c. per minute for the first three minutes and then increased (for the remaining five minutes) to 10.14 grams per 100 c.c. per minute. The vasomotor reaction to cold accordingly, although initially intense, was not especially persistent, giving way to a marked vasodilatation while the contralateral hand was still in the cold water.

The effect of certain poisons on the vasomotor reflexes, as investigated by this method, seemed sufficiently definite to be worthy of mention.

TABLE 27.—CALORIMETRIC MEASUREMENTS IN CASE OF MRS. X.

Time	Right	Left	Room
3:07	29.965	29.97	
3:09	29.995	30.03	27.2
3:10	30.03	30.07	
3:11	30.09	30.13	
3:12	30.16	30.205	
3:13	30.25	30.26	
3:14	30.33	30.34	
3:15	30.45	30.45	27.3
3:16	30.525	30.53	
3:17	30.605	30.625	
3:18	30.68	30.68	
3:19	30.72	30.73*	
3:20	30.755	30.755	
3:21	30.795	30.79	
3:22	.....	30.805	
3:23	.....	30.82	
3:24	.....	30.85	
3:25	.....	30.925	27.3
3:26	.....	30.99	
3:27	.....	31.03	
3:28	.....	31.11	
3:29	.....	31.155	
3:30	.....	31.20	
3:31	.....	31.24	
3:32	.....	31.27	
3:33	.....	31.33	27.4
3:34	.....	31.42	
3:35	.....	31.50	
3:36	.....	31.60	
3:37	.....	31.655	
3:38	.....	31.71	
3:38½	.....	31.74	
3:48	30.625	.....	27.3
3:48½	.....	31.675	

* Here she began to get nervous about the cold water which she saw in preparation being cooled by ice.

Cooling of calorimeters, R., 0.17 C. in twenty-seven minutes, L., 0.065 C. in ten minutes. Volume of right hand 317 c.c., of left hand 326 c.c.

Mrs. X., aged 48, height 4 feet, 10 inches, weight 118 pounds, was admitted at the dispensary May 11, 1911, complaining of a cough that she had had for a week. Her general health was undisturbed. She had no children but

eight miscarriages. She was obviously under the influence of alcohol, and for this reason the blood flow in the hands was examined.

The hands were in bath at 2:59 p. m., in calorimeters at 3:08. At 3:21 the right hand was put into water at 8.4 C. At 3:30 the right hand was put into water at 43 C. At 3:38½ the left hand was taken out of the calorimeter. Mouth temperature 37.35 C. Pulse 96.

The initial flow in this case was good (13.05 grams per 100 c.c. per minute for the right hand and 12.03 grams for the left), even for the relatively high room temperature (27.3 C.). The flow in the left hand was diminished to 4.6 grams when the right was immersed in cold water. After three minutes the vasoconstriction gave place to vasodilatation, the flow increasing to 11.08 grams for the remaining six minutes of immersion of the right hand in cold water. On immersing the right hand in warm water the flow in the left sank to 7.52 grams per 100 c.c. per minute (for three minutes) and then increased to 15.92 grams per 100 c.c. per minute for the remaining five and one-half minutes of immersion, an exceptionally large increase on the top of the good initial flow. The suggestion is that the influence of the alcohol favors reflex vasodilatation of the cutaneous vessels. Evidence of this has also been secured in other cases.

In a case of lead poisoning with no symptoms of peripheral neuritis (John K.) the opposite result was obtained, good crossed vasoconstriction but practically no increase of the initial flow. In other words, the vasomotor mechanism, which under the influence of alcohol was exceptionally ready to respond to appropriate stimuli by vasodilatation, tended, under the influence of lead poisoning, to respond especially to stimuli causing vasoconstriction. In accordance with this the blood pressure was high in John K. (180 mm. Hg). There was no decided anemia and the flow in the hands before the vasomotor reactions were tested was within the normal range (8.96 grams per 100 c.c. per minute for the right hand and 8.81 grams for the left, with room temperature 23 C.).

John K., a laborer, aged 52, was admitted to the City Hospital, May 13. He worked in an automobile factory scraping paint from wheels. For two weeks he had been constipated, with intense pain in the abdomen and the occurrence of vomiting. A lead line was noted on the gums. The lips were red. A blood count showed erythrocytes 4,080,000, leukocytes 6,800. Knee-jerks were present and equal. The grip of the hands was not noticeably weakened. The pupils reacted to light and accommodation. The radial pulse was regular and of high tension. There was some fibrosis of the artery. He was discharged improved on May 25. The blood flow in the hands was examined May 14. He works best with his left hand though he eats and writes with the right.

The hands were in bath at 1:43 p. m., in calorimeters at 1:55½. At 2:09 the left hand was put into water at 8 C. At 2:20 the left hand was put into water at 43.2 C. At 2:33 the right hand was taken out of the calorimeter.

TABLE 28.—Calorimetric Measurements in Case of John K.

Time	Right	Left	Room
1:55	31.00	30.87	
1:57	31.07	30.94	
1:58	31.12	31.00	
2:00	31.21	31.08	
2:01	31.27	31.15	
2:02	31.33	31.21	23.2
2:03	31.39	31.27	
2:04	31.45	31.33	
2:05	31.50	31.39	
2:06	31.56	31.44	23.0
2:07	31.62	31.50*	
2:08	31.65	31.53	
2:09	31.68	31.56	
2:10	31.71		
2:11	31.72		
2:12	31.735		
2:13	31.78	.....	22.4
2:14	31.81		
2:15	31.87		
2:16	31.895		
2:17	31.925	.....	22.3
2:18	31.97		
2:19	31.99		
2:20	32.02		
2:21	32.05		
2:22	32.075	.....	22.3
2:23	32.10		
2:24	32.125		
2:25	32.16		
2:26	32.21		
2:27	32.25	.....	22.3
2:28	32.295		
2:29	32.32		
2:30	32.36		
2:31	32.395	.....	22.3
2:32	32.435		
2:33	32.48	.....	22.4
2:46	32.29	31.10	

* Here he saw ice brought and put into the cold water and seemed to become apprehensive.

Cooling of calorimeters, R., 0.19 C. in thirteen minutes; L., 0.46 C. in thirty-seven minutes. Volume of right hand 475 c.c., of left 472 c.c. Water equivalent of calorimeters with contents, R., 3,475, L., 3,473. Pulse 108.

In another case of lead poisoning (S.), a man aged 40, the flow was 8.05 grams in the right and 8.74 grams in the left hand with room temperature 21.8 C. In this case also the tendency to reflex vasoconstriction was decided, as will be seen by referring to the general table of results.

TABLE 29.—Calorimetric Measurements in Case of S.

Time	Right	Left	Room
3:40	30.03	30.13	
3:41	30.10	30.20	21.9
3:42	30.16	30.26	
3:43	30.20	30.32	
3:44	30.28	30.39	
3:45	30.335	30.45	21.8
3:46	30.40	30.53	
3:47	30.495	30.625	
3:48	30.58	30.71	
3:49	30.63	30.79	
3:50	30.66		
3:51	30.69		
3:52	30.72		
3:53	30.78	.....	21.9
3:54	30.86		
3:55	30.91		
3:56	31.00		
3:57	31.07	.....	21.5
3:58	31.11		
3:59	31.12		
4:00	31.15		
4:01	31.17		
4:02	31.18	.....	21.7
4:03	31.195		
4:04	31.26		
4:05	31.31		
4:06	31.375	.....	22.9
4:07	31.42		
4:08	31.47		
4:10	31.53		
4:11	31.57		
4:12	31.60	.....	22.8
4:13	31.64		
4:14	31.695		
4:27	31.53	30.37	22.5

Cooling of calorimeters, R., 0.165 C. in thirteen minutes, L., 0.42 C. in thirty-eight minutes. Volume of right hand 527 c.c., of left hand 521 c.c. Rectal temperature 38.05 C.

S., a painter, aged 40, height 5 feet, 8½ inches, was admitted to the City Hospital, March 31. He complained of colic, and a blue line was noted around his gums. He had been ill two or three months, and although weak was considerably better. He had no wrist-drop. He was discharged improved April 15. The blood flow in the hands was examined on April 3. Hands were in bath at 3:29 p. m., in calorimeters at 3:39. At 3:49 the left hand was put in water

at 8 C. He felt it very cold. At 4:01 p. m. the left hand was put into water at 43 C. At 4:09 left hand dried and wrapped. At 4:14 the right hand was taken out of calorimeter. Pulse 120.

In Roderick D., a blacksmith, aged 27, excessively addicted to cigaret smoking from boyhood, the flow in the hands was large (12.77 grams for the right and 12.38 grams for the left hand per 100 c.c. per minute, with the rather high room temperature of 26.2 C.). Immersion of the left hand in cold water caused a transient vasoconstriction of the right, the flow falling to 7.73 grams for the first two minutes of immersion. to rise again to 11.03 grams per 100 c.c. per minute for the remaining nine minutes, during which the left hand continued in the cold water. Warm water caused only a small preliminary vasoconstriction, the flow then increasing again though not quite to the high initial value. Scratching the skin with a blunt point caused a well-marked red line which persisted for a considerable time. In this case everything points to the existence of a tendency to vasodilatation, which is in agreement with the observation that nicotin after a preliminary excitation causes depression of the sympathetic nerve cells.

Examination of flow in hands of Roderick D.: Hands in bath at 2:35½ p. m., in calorimeters at 2:47¼. At 2:59 the left hand was put into water at 8 C. He felt it very cold. At 3:10⅙ p. m. the left hand was put into water at 43.5 C. At 3:21 right hand was taken out of calorimeter.

TABLE 30.—Calorimetric Measurements in Case of Roderick D.

Time	Right	Left	Room	Time	Right	Left	Room
2:46½	29.88	29.84		3:06	31.70		
2:48	29.96	29.91		3:07	31.76		
2:49	30.07	30.04	26.2	3:08	31.83		
2:50	30.19	30.20		3:09	31.90	.....	26.3
2:51	30.30	30.31		3:10	31.99		
2:52	30.435	30.44	26.15	3:11	32.06		
2:53	30.565	30.54		3:12	32.11		
2:54	30.65	30.61		3:13	32.17		
2:55	30.78	30.72	26.2	3:14	32.20		
2:56	30.87	30.81		3:15	32.27		
2:57	31.01	30.90		3:16	32.33		
2:58	31.09	30.98	26.3	3:17	32.39		
2:59	31.19	31.065		3:18	32.46	.....	26.4
3:00	31.24			3:19	32.52		
3:01	31.30			3:20	32.56		
3:02	31.37			3:21	32.63	.....	26.5
3:03	31.46			3:22	.....	30.89	
3:04	31.56	.....	26.4	3:34	32.50		
3:05	31.63						

Cooling of calorimeters, R., 0.13 C. in thirteen minutes, L., 0.175 C. in twenty-three minutes. Volume of right hand 535 c.c., of left hand 513 c.c. Water equivalent of calorimeters with contents, R., 3,523, L., 3,505. Mouth temperature 37.4. Pulse 84.

The last case to be cited is that of a young man who shot himself through the brain.

Andrew K., a young foreign laborer, was brought to the City Hospital by the police on May 16, at 4:45 p. m., with a crescent-shaped wound in the scalp on the left side not far from the median line, midway between the glabella and

occipital protuberance. The patient appeared to be in stupor; he did not talk. The right pupil was larger than the left and its outline was irregular. The pupils reacted to light. The external rectus of the right eye was paralyzed. Blood was flowing from the nostrils, but no abrasions were visible in the interior. The tongue protruded in the median line. On the hard palate was a blackish discoloration covering a bullet hole. (It was elicited afterwards that he had shot himself with a revolver.) There was no paralysis; the reflexes were normal. The rectal temperature was 98.8 F. The spinal fluid from the lumbar puncture was bright red, containing much blood. It flowed 120 drops per minute. May 17 the eye grounds were normal. The systolic blood pressure was 140. He voided urine involuntarily. He did not speak, although he was perfectly conscious. There was no Babinski sign. The temperature was 99.8 F. at 8 a. m., and the same at noon. On May 18 he voided urine; the systolic blood pressure was 120. From May 19 to May 21 his condition was the same. On May 24 the systolic pressure was 126, on June 6, 132.

The blood flow in the hands was examined on May 17 and again on June 6. At the first examination he sat quite well in the chair, but was absolutely silent. Hands in bath at 3:05 p. m., in calorimeters at 3:14½, out of calorimeters at 3:28. Pulse 80 (lying down). Room temperature 23.4 C. He kept clutching the stirring feathers occasionally.

TABLE 31.—Calorimetric Measurements in Case of Andrew K.

Time	Right	Left	Room
3:14	31.17	31.17	
3:17	31.22	31.23	
3:18	31.28	31.26	
3:19	31.33	31.33	
3:20	31.39	31.36	
3:21	31.45	31.43	
3:22	31.55	31.52	
3:23	31.61	31.52	
3:24	31.64	31.59	
3:25	31.70	31.63	
3:26	31.77	31.70	
3:27	31.81	31.72	
3:28	31.87	31.76	
3:43	31.69	31.59	

Cooling of calorimeters in fifteen minutes, R., 0.18 C., L., 0.17 C. Volume of right hand 466 c.c., of left 463 c.c. Water equivalent of calorimeters with contents, R., 3,468, L., 3,465. Rectal temperature 37.75 C.

Second examination of Andrew K., June 6: So far he has recovered without symptoms. The right pupil reacts to light equally with the left and now there is little difference in size. The right external rectus is still paralyzed. He will now talk freely. Rectal tmperature 38.65 C. Pulse (sitting) 112. Pulse not large. Hands in bath at 1:44 p. m.

TABLE 32.—Calorimetric Measurements in Second Examination of Andrew K.

Time	Right	Left	Room
1:54	31.68	31.67	
1:56	31.66	31.67	
1:57	31.68	31.70	22.8
1:58	31.70	31.74	
1:59	31.72	31.77	22.8
2:00	31.74	31.825	
2:01	31.78	31.86	
2:02	31.81	31.92	
2:03	31.865	31.97	22.85
2:04	31.895	32.025	
2:05	31.93	32.07	23.0
2:06	31.965	32.12	
2:07	31.99	32.155	
2:08	32.02	32.19	23.1
2:09	32.05	32.23	
2:10	32.08	32.27	23.0
2:11	32.11	32.325	
2:19	32.00		
2:19½	.....	32.205	

Cooling of calorimeters, R., 0.11 C. in eight minutes, L., 0.12 C. in 8½ minutes. Volume of right hand in calorimeter 472 c.c., of left 460 c.c. Water equivalent of calorimeters with contents, R., 3,473, L., 3,463.

Table of Results of Calorimetric Measurements in Twenty-One Cases *

Case	Age	Date	Pulse Rate	Temperature (C) of				Volume of Part in c.c.		Heat Given Off in Gm.-Calories			Blood Flow in Gm. per Min.		Flow per 100 c.c. of Part per Min.		Notes
				Room	Arterial Blood	Calorimeters Right	Calorimeters Left	Right	Left	Right	Left	In Mins.	Right	Left	Right	Left	
Kaspar J. ...	50	5/ 5/11	92	24.2	36.70	29.79	29.66	511	457	1,121	830	8	22.54	16.38	4.80	3.58	Brachial neuritis (rt.). Hands.
				24.2	.....	30.05	.....	...	...	1,121	.....	7	26.76	.....	5.69	.....	Left hand in water at 43 C.
				24.4	.....	30.20	.....	...	...	210	.....	2	17.95	.....	3.82	.....	Left hand in water at 9.5 C.
				24.4	.....	30.33	.....	...	...	1,051	.....	7	26.19	.....	5.55	.....	Left hand still in cold water.
		5/ 8/11	57	25.3	36.70	30.20	30.34	523	478	1,511	1,426	14	18.45	17.79	3.76	3.72	Hands.
				25.4	.....	30.39	.....	...	...	299	.....	4	13.16	.....	2.68	.....	Left hand in water at 42.6 C.
				25.4	....	30.50	.....	...	...	790	.....	7	20.22	.....	4.12	.....	Left hand still in warm water.
				25.3	.....	30.60	.....	...	...	221	.....	3	13.44	.....	2.74	.....	Left hand in water at 8.2 C.
				25.3	.....	30.69	.....	...	...	597	.....	6	18.40	.....	3.75	.....	Left hand still in cold water.
John McH	58	6/ 5/12	...	23.3	37.15	31.10	31.04	494	476	2,199	1,947	19	21.25	18.63	4.30	3.91	Hands.
		6/ 6/12	88	23.3	37.00	31.66	31.54	512	491	2,418	2,058	18	27.95	23.26	5.46	4.74	
				22.9	.....	31.91	.....	...	...	455	.....	6	16.55	.....	3.23	.....	Left hand in water at 43 C.
				23.0	.....	32.03	.....	...	...	981	.....	7	31.33	.....	6.11	.....	Left hand still in warm water.
Frank S.	64	4/23/12	96	21.0	36.70	29.46	29.35	1,020	950	210	414	14	2.30	4.47	0.22	0.47	Feet.
				21.3	.....	.....	29.16	....	...	.....	280	10	.....	4.12	.....	0.43	Right foot in water at 44 C.
				22.1	36.80	30.94	31.09	427	418	756	755	8	17.92	18.36	4.20	4.39	Hands.
		5/15/12	112	22.9	37.10	31.18	31.19	423	423	1,304	1,510	12	20.39	23.57	4.82	5.57	Hands.
Chas. deM.	28	7/10/12	68	30.1	37.00	31.85	31.88	488	479	3,380	3,565	15	48.61	51.57	9.96	10.76	Alcoholic neuritis. Hands.
		(Blood		29.9	.....	.....	32.41	...	...	.....	347	3	.....	28.00	.....	5.84	Right hand in water at 8.1 C.
		pressure,		29.8	.....	.....	32.61	...	...	.....	1,253	7	.....	45.30	.....	9.45	Right hand still in cold water.
		121.74)		29.8	.....	.....	32.81	...	...	.....	313	2	.....	41.50	.....	8.66	Right hand in water at 43.1 C.
				29.7	.....	.....	33.01	...	...	.....	1,357	7	.....	53.99	.....	11.27	Right hand still in warm water.
		7/16/12	84	25.1	37.20	31.73	31.67	479	494	2,574	2,303	11	47.53	42.06	9.92	8.95	Allowing for swelling left hand.
				24.0	37.10	30.91	31.02	1,437	1,452	1,581	2,097	22	12.90	17.40	0.90	1.20	Feet.
Frank D. ...	39	7/23/12	76	25.2	37.10	31.68	31.55	572	542	3,126	3,141	11	58.25	57.16	10.18	10.54	Left wrist drop (pressure).
		(Blood		25.1	.....	.....	32.01	...	...	.....	670	5	.....	29.25	.....	5.40	Right hand in water at 8 C.
		pressure,		25.1	.....	.....	32.14	...	...	.....	1,200	6	.....	44.80	.....	8,26	Right hand still in cold water.
		133.86)		25.2	.....	.....	32.38	...	...	.....	390	5	.....	18.36	.....	3.38	Right hand in water at 43 C.
				25.2	.....	.....	32.63	...	...	.....	1,886	8	.....	58.60	.....	10.81	Right hand still in warm water.
Stanislas C.	32	4/19/11	72	23.7	36.8	30.16	29.91	486	442	1,220	242	6	34.02	6.50	7.0	1.47	Hands.
				23.7	.....	30.46	.....	...	...	871	.....	4	38.17	.....	7.85	.....	Left hand in water at 12 C.
				23.6	.....	30.69	.....	...	...	766	.....	3	46.42	.....	9.55	.....	Left hand dried and wrapped.
				23.5	.....	30.99	.....	...	...	1,568	.....	6	49.98	.....	10.28	.....	Left hand in water at 43.5 C.
				23.7	.....	31.39	.....	...	...	1,463	.....	6	50.08	.....	10.30	.....	Left hand in water at 9 C.
				23.5	.....	31.68	.....	...	...	731	.....	3	52.89	.....	10.88	.....	Left hand dried and wrapped.
Mrs. Eva M.	56	4/16/12	104	23.0	37.45	30.75	30.58	334	328	2,286	1,611	18	21.06	14.47	6.30	4.38	Left hemiplegia. Hands.
George H. ..	40	7/18/12	68	26.5	36.95	31.76	31.96	464	500	1,889	2,604	12	33.70	49.10	7.26	9.82	Right hemiplegia. Hands.
		(Blood		26.7	.....	32.01	.....	...	...	312	.....	3	23.39	.....	5.04	.....	Left hand in water at 8 C.
		pressure,		26.4	.....	32.17	.....	...	...	1,109	.....	7	36.82	.....	7.93	.....	Left hand still in cold water.
		91.83)		26.4	.....	32.41	.....	...	...	1,126	.....	10	27.55	.....	5.94	.....	Left hand in water at 43 C.
		7/25/12	86	25.5	36.90	31.65	31.83	455	497	2,421	3,597	12	42.70	65.69	9.38	13.21	Hands.
				24.7	.....	31.06	31.07	1,299	1,265	1,335	1,410	12	21.16	22.39	1.63	1.77	Feet.

* The tabular summary of results on A. O. H., Casimir M., John S., Mrs. M. C., Max B., Mrs. Mary N., C. and Abe K. is given in Table II, Heart, 1911, iii, 84.

Dennis H. . .	41	4/11/12 (Blood pressure, 118)	80	25.5	36.8	30.64	30.66	505	451	1,995	1,590	17	21.17	16.92	4.19	3.75	Left hemiplegia. Hands.
				25.5	.....	30.47	30.51	...	...	490	276	6	14.33	8.13	2.84	1.80	For the first six minutes.
				25.4	.....	.....	30.87	...	...	.....	588	7	.....	15.74	.....	3.49	Right hand in water at 8 C.
				25.4	.....	.....	31.03	...	...	.....	967	7	.....	26.60	.....	5.90	Right hand still in cold water.
				25.4	.....	.....	31.18	...	...	.....	484	4	.....	23.92	.....	5.30	Right hand in water at 43 C.
				25.4	.....	.....	31.33	...	...	.....	967	8	.....	24.55	.....	5.51	Right hand still in warm water.
Joseph S. . . .	54	8/ 7/12	124	25.0	37.75	31.12	31.14	1,110	1,104	594	686	12	8.30	9.61	0.76	0.88	Feet. Tabes.
				25.0	37.85	31.43	31.30	425	441	1,872	1,465	13	24.92	19.11	5.86	4.33	Hands.
				25.0	.....	31.68	.....	...	...	492	.....	4	22.15	.....	5.21	.....	Left hand put in water at 8.4 C.
				25.0	.....	31.83	.....	...	...	1,002	.....	8	23.11	.....	5.43	.....	Left hand still in cold water.
				25.0	.....	32.00	.....	...	...	584	.....	5	22.18	.....	5.22	.....	Left hand in water at 42.8 C.
				25.2	.....	32.12	.....	...	...	721	.....	6	23.30	.....	5.48	.....	Left hand still in warm water.
W. B. C. . .	57	11/11/14	84	21.5	36.30	30.98	31.02	925	943	384	624	16	5.01	8.27	0.54	0.87	Feet. Tabes.
				21.8	.....	30.85	.....	...	...	413	.....	12	7.01	.....	0.75	.....	Left foot in water at 44.1 C.
				22.9	36.40	31.82	31.81	380	388	850	810	10	20.62	19.60	5.42	5.05	Hands.
				22.9	.....	31.88	.....	...	...	310	.....	5	15.24	.....	4.01	.....	Left hand in water at 44.5 C.
				22.8	.....	31.95	.....	...	...	845	.....	9	23.44	.....	6.16	.....	Left hand still in warm water.
				22.8	.....	32.01	.....	...	...	49	.....	1	12.40	.....	3.26	.....	Left hand in water at 13 C.
				22.6	.....	32.05	.....	...	...	631	.....	8	20.14	.....	5.30	.....	Left hand still in cold water.
Gabriel M. . .	41	11/17/14	92	22.6	36.76	31.50	31.50	431	395	390	491	19	4.33	5.44	1.00	1.37	Tabes. Hands.
		11/19/14	100	23.9	36.70	31.74	31.64	424	407	827	797	15	12.35	11.66	2.91	2.86	Hands.
				24.3	.....	31.79	.....	...	...	577	.....	10	13.05	.....	3.07	.....	Left hand in water at 43 C.
				22.8	36.60	31.18	31.12	1,117	1,092	369	404	12	6.30	6.82	0.56	0.62	Feet.
				23.0	.....	.....	30.99	...	...	.....	1,085	22	.....	9.76	.....	0.89	Right foot in water at 43.5 C.
		11/24/14	108	22.1	37.05	31.42	31.36	425	390	478	461	8	11.79	11.25	2.77	2.88	Hands.
				22.2	36.95	30.88	30.94	1,092	1,087	806	605	14	10.53	7.98	0.96	0.73	Feet.
				22.5	.....	.....	30.88	...	...	.....	155	4	.....	7.09	.....	0.65	Right foot in water at 43 C.
				22.6	.....	.....	30.86	...	...	.....	551	10	.....	10.05	.....	0.92	Right foot still in warm water.
				22.8	.....	.....	30.84	...	...	.....	202	4	.....	9.18	.....	0.84	Right foot in water at 8.7 C.
				23.0	.....	.....	30.80	...	...	.....	421	10	.....	7.60	.....	0.70	Right foot still in cold water.
John M. . . .	45	12/ 3/14	116	24.2	37.05	31.46	31.52	1,067	1,042	960	936	14	13.62	13.43	1.27	1.28	Tabes. Feet.
				24.6	.....	.....	31.55	...	...	.....	592	12	.....	9.95	.....	0.95	Right foot in water at 9.5 C.
				24.8	.....	.....	31.57	...	...	.....	247	4	.....	12.52	.....	1.17	Right foot in water at 42.6 C.
				24.9	.....	.....	31.63	...	...	.....	839	10	.....	17.20	.....	1.65	Right foot still in warm water.
		12/ 8/14	96	24.0	37.15	31.90	31.92	426	399	1,065	1,160	8	28.14	30.22	6.60	7.57	Hands.
				24.2	.....	32.06	.....	...	...	629	.....	5	27.46	.....	6.46	.....	Left hand in water at 8 C.
				24.5	.....	32.20	.....	...	...	804	.....	5	36.09	.....	8.47	.....	Left hand still in cold water.
				24.5	.....	32.43	.....	...	...	1,432	.....	9	37.45	.....	8.79	.....	Left hand in water at 43.1 C.
				24.7	37.05	31.98	32.06	1,006	1,001	621	706	10	13.60	15.72	1.35	1.57	Feet.
				24.7	.....	.....	32.05	...	...	.....	880	14	.....	13.96	.....	1.39	Right foot in water at 8.3 C.
Joseph K. . . .	48	6/26/12	...	27.3	37.05	31.44	31.43	495	479	2,234	2,121	10	44.24	41.93	8.94	8.75	Hands.
				27.3	.....	31.88	.....	...	...	1,309	.....	10	28.13	.....	5.68	.....	Left hand in water at 8.4 C.
				27.5	.....	32.16	.....	...	...	1,187	.....	7	38.53	.....	7.78	.....	Left hand in water at 43 C.
				27.5	.....	32.42	.....	...	...	977	.....	4	58.61	.....	11.84	.....	Left hand still in warm water.
				26.4	36.95	31.05	30.99	1,280	1,292	537	586	16	6.34	6.85	0.50	0.54	Feet.
				26.7	.....	.....	30.98	...	...	.....	363	10	.....	6.75	.....	0.53	Right foot in water at 43 C.

Table of Results of Calorimetric Measurements in Twenty-One Cases —(*Continued*)

Case	Age	Date	Pulse Rate	Temperature (C) of: Room	Arterial Blood	Calorimeters: Right	Calorimeters: Left	Volume of Part in c.c.: Right	Left	Heat Given Off in Gm.-Calories: Right	Left	In Mins.	Blood Flow in Gm. per Min.: Right	Left	Flow per 100 c.c. of Part per Min.: Right	Left	Notes
Fred L.	22	11/18/12	88	22.0	37.2	30.56	30.57	385	377	1,626	1,403	13	20.93	18.09	5.43	4.80	Cerebral tumor. Hands.
						30.75	.....	...	...	187	.....	2	16.10	.....	4.18	.....	Left hand in water at 43 C.
						30.97	.....	...	...	1,787	.....	10	31.87	.....	8.28	.....	Left hand still in warm water.
				22.8	.....	31.19	.....	...	...	285	.....	6	8.78	.....	2.28	.....	Left hand in water at 11.2 C.
				22.3	.....	31.25	.....	...	...	599	.....	6	18.64	.....	4.84	.....	Left hand still in cold water.
		11/26/12	100	21.4	37.25	31.35	31.33	389	380	1,652	1,446	13	23.93	20.87	6.15	5.49	Hands.
				20.9	.....	.....	31.48	...	...	.....	320	3	.....	12.51	.....	3.29	Right hand in water at 43 C.
				20.7	.....	.....	31.65	...	...	.....	1,396	8	.....	34.62	.....	9.11	Right hand still in warm water.
				20.7	.....	.....	31.80	...	...	.....	747	11	.....	13.84	.....	3.64	Right hand in water at 10.5 C.
				20.7	.....	.....	31.91	...	...	.....	1,179	11	.....	22.30	.....	5.87	Right hand in water at 43 C.
J. S.	..	4/ 5/12	92	25.9	37.3	30.60	30.64	389	358	749	811	6	20.70	22.55	5.32	6.30	Tetanus. Hands.
				26.2	.....	30.71	.....	...	...	307	.....	4	12.94	.....	3.32	.....	Left hand in water at 43.5 C.
				26.0	.....	30.90	.....	...	...	1,226	.....	6	35.47	.....	9.09	.....	Left hand still in warm water.
				26.0	.....	31.08	.....	...	...	255	.....	3	15.18	.....	3.90	.....	Left hand in water at 7 C.
				25.8	.....	31.24	.....	...	...	1,073	.....	5	39.34	.....	10.14	.....	Left hand still in cold water.
Mrs. X.	48	5/11/11	96	27.3	37.35	30.44	30.46	317	326	2,579	2,432	10	41.47	39.23	13.08	12.03	Alcoholic intoxication. Hands.
				27.3	.....	.....	30.82	...	...	.....	268	3	.....	15.22	.....	4.60	Right hand in water at 8.4 C.
				27.3	.....	.....	31.05	...	...	.....	1,309	6	.....	38.48	.....	11.80	Right hand still in cold water.
				27.4	.....	.....	31.27	...	...	.....	403	3	.....	24.57	.....	7.54	Right hand in water at 43 C.
							31.54	...	...	.....	1,493	5½	.....	51.92	.....	15.92	Right hand still in warm water.
John K.	52	5/14/12	108	23.0	37.2	31.38	31.25	475	472	2,676	2,674	12	42.57	41.61	8.96	8.81	Lead poisoning. Hands.
		(Blood		22.4	.....	31.71	.....	...	...	313	.....	3	21.11	.....	4.44	.....	Left hand in water at 8 C.
		pressure,		22.3	.....	31.88	.....	...	...	1,390	.....	8	36.29	.....	7.64	.....	Left hand still in cold water.
		180)		22.3	.....	32.07	.....	...	...	556	.....	4	30.10	.....	6.34	.....	Left hand in water at 43.2 C.
				22.3	.....	32.30	.....	...	...	1,702	.....	9	42.88	.....	9.02	.....	Left hand still in warm water.
S.	40	4/ 3/12	120	21.8	37.6	30.33	30.46	527	521	2,497	2,634	9	42.40	45.54	8.05	8.74	Lead poisoning. Hands.
						30.68	.....	...	...	440	.....	3	23.55	.....	4.47	.....	Left hand in water at 8 C.
				21.9	.....	30.92	.....	...	...	1,635	.....	6	45.33	.....	8.60	.....	Left hand still in cold water.
				21.5	.....	31.14	.....	...	...	335	.....	3	19.21	.....	3.64	.....	Left hand still in cold water.
				21.7	.....	31.18	.....	...	...	176	.....	2	15.23	.....	2.89	.....	Left hand in water at 43 C.
				22.9	.....	31.35	.....	...	...	1,372	.....	6	40.65	.....	7.71	.....	Left hand still in warm water.
				22.8	.....	31.60	.....	...	...	879	.....	5	32.55	.....	6.18	.....	Left hand dried and wrapped.
Roderick D.	27	5/10/11	84	26.2	37.4	30.58	30.49	535	513	4,615	4,346	11	68.35	63.54	12.77	12.38	Tobacco. Hands.
				26.3	.....	31.25	.....	...	...	458	.....	2	41.37	.....	7.73	.....	Left hand in water at 8 C.
				26.4	.....	31.65	.....	...	...	2,748	.....	9	59.00	.....	11.03	.....	Left hand still in cold water.
				26.4	.....	32.10	.....	...	...	880	.....	4	46.12	.....	8.62	.....	Left hand in water at 43.5 C.
				26.4	.....	32.42	.....	...	...	1,762	.....	7	56.16	.....	10.49	.....	Left hand still in warm water.
Andrew K. ..	..	5/17/12	80	23.5	37.25	31.54	31.50	466	463	2,687	2,252	11	47.53	39.66	10.20	8.56	Bullet wound of brain. Hands.
		6/ 6/12	112	23.0	38.15	31.95	32.09	472	460	1,615	2,078	10	28.94	38.10	6.13	8.28	Blood pressure 132.

The patient was discharged cured. He was readmitted July 31 suffering from rheumatism and chronic alcoholism and was discharged "improved" on August 27.

At the first examination of Andrew K., made not much more than twenty-four hours after he was brought into the hospital, the blood flow in the right hand was 10.20 grams per 100 c.c. per minute and in the left 8.56 grams, with room temperature 23.5 C. At the second examination, nearly three weeks later, the flows were 6.13 grams and 8.28 grams respectively for the right and left hands, with room temperature 23 C. He had some fever at the time of the second examination which is perhaps associated with the somewhat smaller flows.[11] It will be noted that on both occasions a distinct difference existed in the rate of flow in the two hands. The fact that there is no constancy in this difference, the greater flow being in the right hand at the first examination, in the left hand at the second, indicates that the differences are of vasomotor origin, but it is impossible to say whether they are related in any way to the brain injury. Our observations on chronic alcoholism, for which in the sequel this man was again admitted to the hospital, would perhaps suggest this rather than the brain lesion as the condition associated with the vasomotor instability. There is, of course, no obvious reason why a bullet wound through a cerebral hemisphere which occasioned no paralysis should cause a permanent difference of flow between the hands, nor indeed any obvious reason why so long as it was not associated with general symptoms it should produce any effect whatever on the circulation in the extremities. As a matter of fact, the average hand flows at the two examinations are quite within the normal range.

SUMMARY

1. In early unilateral brachial neuritis the blood flow in the affected hand was found to be decidedly greater than in the normal hand. This is interpreted as due to partial paralysis of the vasoconstrictor fibers in the nerves involved in the pathologic process.

In long-standing unilateral neuritis with decided atrophy of the affected part, the blood flow is less on the side of the lesion than on the normal side. There is some evidence that one factor in the diminution of the flow may be a change in the walls of the arteries consequent on the injury to the vasomotor nerves, which leads to diminution of the lumen. This may be considered an adaptive change correlated with the diminished function of the part. The diminution in the flow may also be due to the regaining of vascular tone by the paralyzed part, even in the absence of regeneration of its nerve supply.

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11. Jour. Exper Med., 1913, xviii, 372.

In peripheral neuritis affecting mainly muscular nerves, the changes in the blood flow of the hands and feet are not so conspicuous, as when the cutaneous nerves are also involved, since a large portion of the total flow in these parts must belong to the skin.

2. In hemiplegia there is, in general, a marked deficiency in the blood flow in the paralyzed members. Considerable differences, however, exist in different cases in this regard, and also in the extent to which the vasomotor reflexes from the normal to the paralyzed part are affected. Whether these differences depend at all on the position of the lesion or are associated with the duration and completeness of the paralysis has not been determined. There is some evidence that reflex vasoconstriction is more easily produced in the paralyzed parts than reflex vasodilatation.

3. In tabes, the blood flow in both hands and feet, but especially in the feet, has been found decidedly subnormal and the vasomotor reflexes feeble.

4. In lead poisoning (without paralysis), the tendency to reflex vasoconstriction was conspicuous. This seemed to be the case also in alcoholic neuritis. In alcoholic intoxication and in a case of excessive cigaret smoking, the opposite was observed, namely, a tendency to marked reflex vasodilatation.

5. It is suggested that, in some cases, examination of the blood flow might aid in the detection of malingering, when the attempt is made to simulate certain neuropathologic conditions. It seems probable that the differential diagnosis, for instance, between such conditions as cerebral hemorrhage and alcoholic intoxication, or between hysterical palsy and paralysis due to an organic lesion, in doubtful cases might be facilitated by blood-flow measurements.

I wish to express my obligations to the staffs of the City Hospital and of Lakeside Hospital for aid without which this investigation could not have been carried out.

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STUDIES ON THE CIRCULATION IN MAN

XIV. THE CHANGE PRODUCED IN THE BLOODFLOW (IN THE HANDS) UNDER THE INFLUENCE OF DIGITALIS IN CASES OF AURICULAR FIBRILLATION.

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The marked beneficial action of digitalis in auricular fibrillation has been insisted upon by Mackenzie (Heart, ii, 265, 1911), Cushny (Heart, iv, 33, 1912), and other observers. We have thought it of interest to determine whether any effect can be shown to take place in the rate of the bloodflow through the hands, and have obtained a positive result in 3 cases, the flow being distinctly increased. The flow in patients under hospital regimen varies so little from day to day when the experimental conditions, especially the external temperature, are properly controlled, and no obvious clinical change has occurred, that it was not necessary to have recourse to intravenous injection of strophanthin. The administration of m20 of the tincture of digitalis every four hours *per os* was found sufficient to produce definite and prompt effects.

Thus in John Di C.,[1] a man aged 38 years, the flow immediately after admission to the hospital, before he had gone to bed, was 6.23 gm. per 100 cc. of part per minute for the right hand and 6.87 gm. for the left hand (average for the two hands 6.55 gm.) with an average room temperature of 24.8°C. Digitalis was begun about 24 hours after the bloodflow examination. Twenty hours after the first dose, the flow was found to be 8.56 gm. per 100 cc. of part per minute for the right and 8.28 gm. for the left hand

[1] With one exception the cases studied were from the service of Dr. E. P. Carter, at the city hospital, to whom we are indebted for many courtesies.

(average for the two hands 8.42 gm.), with average room temperature 24.0°C. Twenty-four hours later, when he had received in all m220 of the tincture, the flows came out 10.80 gm. and 10.94 gm. for the right and left hands respectively (average 10.87 gm., with room temperature 25.0°C. His clinical condition had steadily improved, a distinct improvement being noted at the first examination after digitalis. At a fourth examination, eight days after admission, digitalis treatment being continued, the flows were 8.32 gm. and 8.26 gm. for the right and left hands respectively (average 8.29 gm.) wilth room temperature 26°C.

At the fifth examination, 11 days after admission, the flows were 8.02 gm. and 8.26 gm. for the right and left hands respectively (average 8.14 gm.) with room temperature 24.1°. These flows are still well above the initial level before digitalis was commenced, in spite of the fact that he complained of gastric discomfort. This was the last bloodflow examination in the case, and the digitalis was discontinued.

It may, of course, be supposed that some part of the improvement in the bloodflow is associated with the rest in bed and that the drug treatment is not necessarily responsible.

However, it is unlikely that the decided effect observed at the second and still more at the third examination could have been in any important degree due to rest alone. For the programme of making a second examination before digitalis was given had to be interrupted by the very circumstance that under rest alone the patient became so bad that digitalis had to be begun, 30 hours after his admission and before the control examination could be duplicated.

In the next case (Andrew S.) this objection was taken account of by keeping the patient under observation for two days in the hospital, making a bloodflow measurement on each day, and then beginning the administration of digitalis.

Andrew S., a man aged 65 years, had on the day of admission a flow of 6.79 gm. per 100 cc. of part per minute in the right hand and the same in the left hand, with room temperature 23.7°C. On the next day the flows were 6.96 gm. for the right and 6.70 gm. for the left hand (average 6.83 gm.) with room

temperature 24.2°C., that is to say, exactly the same as on the day of admission. Clinically there was little if any change in his condition. Rest alone had not caused any change in the flow. It is proper to point out that such an exact correspondence on two successive days is merely accidental. But it can be safely concluded that any effect produced by rest was in this patient slight during these first 48 hours. Digitalis treatment was begun immediately after the second examination. On the following day (May 7), after he had received m120 of the tincture, the flow in the right hand was 8.79 gm., and in the left 8.46 gm. (average 8.62 gm.) with average room temperature 24.7°C. On May 8, the flows were 7.53 gm. and 7.60 gm. for the right and left hands respectively (average 7.57 gm.) with room temperature 24.2°C. On May 10, when he had received altogether one ounce of the tincture, the flow in the right hand came out 10.17 gm. and in the left 9.87 gm. (average 10.02 gm.) with room temperature 24.9°C. His clinical condition was much improved.

On May 12, the flow in the right hand was 8.97 gm. and in the left 8.33 (average 8.65 gm.) with room temperature 26.2°C. The patient felt well except, as he said, that the medicine (digitalis) "made his heart beat too strong." This was the last examination of the case and digitalis was discontinued on this day.

In a third case (E. P. W.),[2] a prompt reaction to digitalis was also observed, but the patient developed pneumonia and only three examinations were possible. Three days after admission to the hospital and before digitalis had been administered, the bloodflow in the right hand was 6.9 gm. per 100 cc. per minute, and in the left 7.4 gm. (average 7.14 gm.) with room temperature 20.0°C. Digitalis was then begun and on the next day the flows came out 11.05 gm. for the right hand and 10.95 gm. for the left (average 11.0 gm.) with room temperature 19.8°C. It was observed that in E. P. W. the effect of the digitalis was very promptly manifested, the pulse rate declining very soon and

[2] This case was examined by one of us at the National Hospital for Diseases of the Heart, London, through the courtesy of Dr. Russell Wells.

diuresis becoming marked before the bloodflow measurement was made. Four days later, digitalis being continued, the flow in the right hand was 10.66 gm. and in the left 11.43 gm. per 100 cc. per minute (average 11.03 gm.) for the first 7 minutes in the calorimeters, with room temperature 17.5°C. Towards the end of the examination he began to feel chilly, the heating plant being out of order, and the bloodflow in the hands promptly diminished to 7.56 gm. per 100 cc. per minute for the right hand and 7.65 for the left (average 7.61 gm.) for the last 5 minutes in the calorimeters.

Putting the observations on these three cases together, the conclusion seems warranted that in auricular fibrillation when the heart responds in the typical way to digitalis the rate of the bloodflow in the peripheral vessels is increased. As has been pointed out elsewhere (Archives of Int. Med., 1914, xiii, 1), an increased hand or foot flow, where no evidence of a purely local vasodilatation is present, must in general be interpreted as indicating an increased heart output.

It scarcely needs to be pointed out that if digitalis produces this effect, the hand flow need not be expected to go on increasing as long as the digitalis treatment is continued. On the contrary, and our observations lend support to this conclusion, it is to be assumed that a maximum effect will be reached which will be greater or less, and more or less promptly attained in different cases. Also it may be assumed that the continuance of digitalis beyond a certain point may diminish the flow instead of increasing it. Discontinuance of the digitalis will then be followed by an increased flow.

It is known also that in some cases in which auricular fibrillation is present, there is either no response to digitalis so far as the heart's action is concerned, or the response is much less striking than in the majority of cases. Our fourth case (C. R.), a syphilitic, seems to belong to this group. He had been treated with digitalis for a considerable time before the bloodflow observations were begun. The digitalis treatment had been combined with anti-syphilitic medication (mercury and salvarsan) and the latter was continued after digitalis was stopped. It was

not considered that he had responded well to digitalis. In any case after it was stopped his pulse did not become more irregular or more frequent, and he felt better at each examination. Although it is not desired to lay stress on this, it is of interest that there was no diminution in the hand flow after discontinuance of the digitalis treatment, but on the contrary a progressive, although moderate, increase. Thus at the first examination (May 19), after about 5 weeks' treatment, during which time the digitalis had been once discontinued for an interval of a few days, the flow in the right hand was 5.39 gm. per 100 cc. per minute, and in the left 4.56 gm. (average 4.98 gm.) with room temperature 24.5°C. Two days later digitalis was discontinued and on May 24 the flows were 6.59 gm. and 6.08 gm. for the right and left hands respectively (average 6.33 gm.) with room temperature 24.3°C. On May 27 the right hand had a flow of 7.12 gm. per 100 cc. per minute and the left hand a flow of 5.84 gm. (average 6.48 gm.) with room temperature 24.6°C. On June 1, when he was feeling so well that he wished to go home, the flows came out 7.78 gm. and 7.05 gm. for the right and left hands respectively (average 7.41 gm.) with room temperature 25.9°C. Of course the somewhat higher room temperature on this occasion might have been partly responsible for the increased flow, but it is unlikely that this was an important factor since the pulse rate was not increased.

The man left the hospital on June 3, and returned on June 8 feeling worse, with an increased pulse rate, dyspnoea on exertion, cough, and vomiting. The bloodflow in the hands three hours after his readmission was 6.68 gm. and 7.27 gm. for the right and left hands respectively (average 6.97 gm.), with room temperature 25.3°C. Digitalis was begun on the night of June 9 to 10, and the bloodflow again examined on June 11. He was feeling somewhat better, but he still had a good deal of cough, some dyspnoea, and his pulse, although the rate was somewhat diminished both at the apex and the wrist, was not markedly improved. The flow came out for the right hand 6.82 gm. and for the left 7.26 gm. (average 7.04 gm.) with room temperature 25.5°C., practically the same as at the last examination.

On June 12, digitalis having been continued in the meantime, a careful examination revealed no material improvement in the pulse, although the patient felt somewhat better.

On June 15, after he had received in all one ounce, three drachms of a tincture known to be active in other cases, the average hand flow was only 4.45 gm. per 100 cc. per minute with room temperature 25.0°C., i.e., about the same as at the end of the previous course of digitalis. The weather was rather cool and the room had to be heated artificially to some extent to obtain a room temperature comparable to that in the other observations. His hands felt distinctly cool. The pulse frequency at the wrist was only about half of the apex rate, showing that a very large proportion of the ventricular beats were too feeble to be detected in the radial. The radial pulse did not show the decided increase in volume, especially of the stronger beats under digitalis in the other three cases. No attempt has been made in these observations to separate a possible vasoconstrictor action of the drug on the bloodflow in the extremities from the effect of an increased heart output. If both effects are present in the three cases which exhibited a distinctly increased hand flow, it is to be assumed that the action on the heart more than offset vasoconstrictor action. It is conceivable that in different cases the relative magnitude of the two effects may be different. If both effects, for instance, were produced in C. R. vaso-constriction in the hands must have more than offset any increase in the output.

SUMMARY

In three cases with auricular fibrillation, the bloodflow in the hands was promptly and decidedly increased after the administration of digitalis. In a fourth case, which had not been considered to respond well to digitalis, the hand flow was somewhat increased when the drug was stopped after a rather long course of it. Digitalis having been again begun, the hand flow at the end of a week was again found to be diminished.

EXTRACTS FROM CASE HISTORIES

John Di C., an Italian laborer, aged 38 years, height 5 feet, $2\frac{1}{2}$ inches, weight 131 pounds, admitted to the City Hospital May 24, 1915. Diagnosis: rheumatic myocarditis (and endocarditis) with auricular fibrillation. He had rheumatism at 12 years of age and two or three times since. He was in hospital nine years ago with heart trouble. He has had dizziness occasionally for the past two years, lasting only a minute or two at a time. His present illness began on Easter Sunday with pain in the chest. The feet were swollen for the following three or four days. He has not worked for the past six months on account of his illness. He cannot sleep because of pain and palpitation about the heart.

Heart. Left border of cardiac dullness at the anterior axillary line. No enlargement upward or to the right. Auscultation reveals a gross irregularity in the heart's action, some contractions being very weak with the sounds scarcely audible, others very forcible with loud and distinct sounds. Apex rate 135. Radial pulse unequal and irregular, with no predictable sequence. Blood pressure, average systolic 105.

The bloodflow in the hands was examined on May 24 immediately after his admission and before he had gone to bed. He had been resting in bed at home for a good many days before coming to the hospital.

May 25, Apex pulse rate 130, radial rate 110. Blood, leucocytes 15,000, haemoglobin 80 per cent, Wassermann test negative. Average systolic blood pressure 132. He got so bad on May 25 that it was necessary to start the administration of digitalis (mxx every four hours) at 11 p.m.

Urine: Trace of albumin with a few hyalin and granular casts.

The bloodflow was again examined on May 26. He said he felt better. Pulse 120 at the wrist.

May 27. Another bloodflow examination was made. He feels stronger today than at any time since he entered the hospital.

May 29. Apex rate 87, radial rate 85.

June 1. Pulse at wrist 60 and fairly regular. He feels fairly well. A bloodflow examination was made on this day.

June 4. The bloodflow was again examined today. He said he was feeling bad. He had just eaten his dinner, which he enjoyed, but he said "his stomach did not like it." Pulse at wrist 70. Figure 1 is an electrocardiogram from John Di C.

Andrew S., a Hungarian laborer, aged 65 years, admitted to the City Hospital on May 5, 1915. Diagnosis: chronic myocarditis with auricular fibrillation and arteriosclerosis. There is dyspnoea, and oedema of the legs below the knee. No cyanosis. Thorax emphysematous. Crepitant râles throughout, especially at the bases.

Heart: upper border of dulness third rib; left border one and one-half fingers' breadth outside the nipple line; right border inside the right sternal margin. Heart sounds faint. Systolic murmur at the apex. Radial pulse grossly irregular in rhythm and amplitude. Pulse rate at apex 150, radial 120.

The bloodflow was examined on day of admission. He is left-handed in his work, but in eating uses knife in the right hand. On May 6 another bloodflow examination was made. He has not had any drug

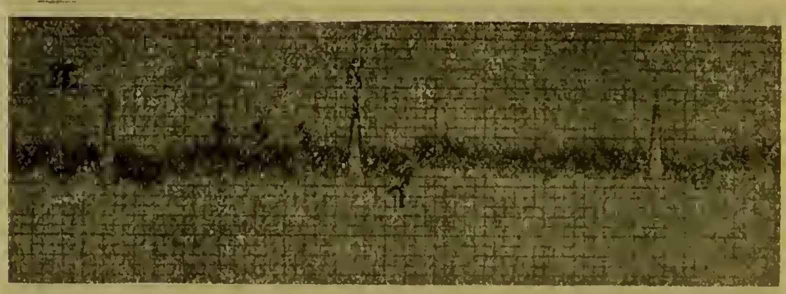

Fig. I. Case 1. Lead 2. Note the absence of the P summits and the marked irregularity of the ventricular deflection R.

treatment since admission. He still complains of dyspnoea. Blood, leucocytes 8200, haemoglobin 79 per cent. The highest radial pulse rate (120) was noted at 8 p.m. on this day. Digitalis (mxx of the tincture every 4 hours night and day) was begun at 4 p.m., on May 6, and continued till the evening of May 12. He had been in the hospital on a previous occasion and had then responded well to digitalis. Bloodflow examinations were made on May 7, 8, 10 and 12. On May 7 he said he felt better, though there was still some dyspnoea, and swelling of feet. He said he knew the "medicine" helped him. On May 8 his condition was much the same as on May 7. On May 10 further improvement was noted. Average systolic blood pressure 110.

On May 12 he said the medicine (digitalis) made his heart beat too strong. Otherwise he felt well. Still some swelling of the feet. The maximum radial pulse recorded on May 10–12 was 98.

E. P. W., a commercial traveller, aged 45 years, admitted to the hospital February 16, 1914. His illness began in October, 1909. Since then he has had gradually increasing symptoms—dyspnoea, palpitation, pain, cough and oedema—and he has been only able to work intermittently. His present breakdown dates from Christmas, 1913, since when his condition has rapidly grown worse.

Condition on admission. Dyspnoea, ascites, oedema marked in the lower extremities. Radial pulse 120–100, rhythm quite muscular. Arterial wall palpable. Jugular vein engorged. Limits of cardiac dulness, right 5 cm. from the midsternal line, left 15 cm. from midsternal line in fifth interspace. The electrocardiogram shows the characters of auricular fibrillation. There is some impairment of resonance at the bases of both lungs and many crepitations and râles. Liver enlarged, three inches below costal margin. The left arm has been weaker than the right and stiff since he was vaccinated in childhood. The first examination of the bloodflow in the hands was made on February 19. Digitalis was begun on the morning of February 20. He had been on digitalis some time before his admission to the hospital, and the effect of the present course was very promptly manifested, the pulse rate declining very soon and diuresis becoming marked before the second bloodflow examination was made on the afternoon of February 20. The digitalis was continued and a third bloodflow examination made on February 24.

C. R., a man aged 30 years, height 5 feet 10½ inches, weight 157 pounds, admitted to City Hospital April 15, 1915. He has worked as a collector and also at night as instructor in a gymnasium. He has had to give up his work on account of heart trouble. He had gonorrhea twice, 10 or 12 years ago, and chancre 6 or 7 years ago, when he underwent only local treatment for the sore. He has headache when he exercises too much, and dizziness at times, also dyspnoea and blurring of the sight. There is a slight oedema of the lower extremities below the knees. Blood, leucocytes 17,000; haemoglobin 85, Wassermann strongly positive.

Heart: left border 5 cm. outside mid-clavicular line; right border 2 cm. to right of right sternal margin. Upper border at third rib. A faint blowing systolic murmur is heard over the apex; otherwise the sounds are clear. The heart rate is grossly irregular and the sounds vary in intensity.

Diagnosis, syphilitic myocarditis with auricular fibrillation. He was put on digitalis and also on mercury (biniodide), and increasing doses of

potassium iodide. Apex rate 160, radial rate 110. Average systolic pressure 105. On May 2, the radial rate was 60, the apex rate 107. On June 1, the apex rate was 80 and the radial 72. Figure 2 is a polygraph tracing from C. R.

The bloodflow in the hands was measured on May 19. On May 21 digitalis was stopped, but the mercurial treatment was continued. On May 24 a second bloodflow examination was made. The patient said he felt better than at the last examination. A third examination was made on May 27. He was feeling very well and had been out in the

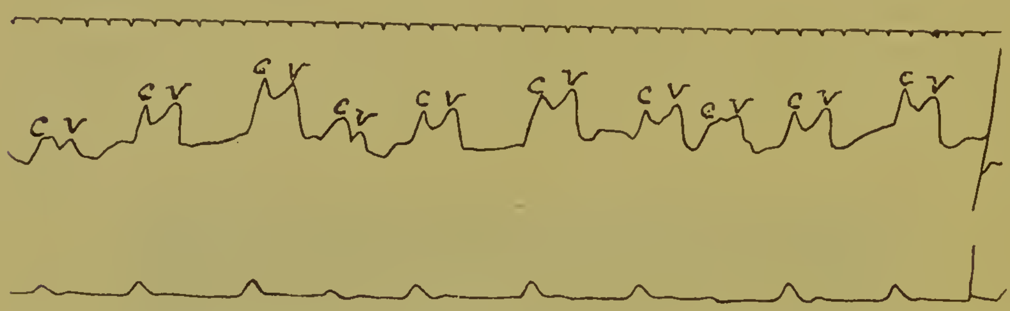

Fig. II. Tracing taken with Mackenzie polygraph from C. R. Upper curve from jugular, lower from radial artery. Time trace, fifths of a second.

yard. The maximum pulse rate at the wrist since digitalis was discontinued has been 84. Today it was 68. A fourth bloodflow examination was made on June 1. The pulse rate at the wrist is 72, at the apex 80. Since May 28 the pulse rate has varied from 84 to 60. He feels so well that he wants to go home. He went home on June 3, but returned to the hospital on June 8 complaining of dyspnoea and weakness, and that his stomach was upset. Apex rate 150, radial 115 on admission at 11 a.m. The bloodflow was examined on June 8, June 11 and June 15.

PROTOCOLS OF BLOODFLOW MEASUREMENTS

First examination of John Di C., May 24. Hands in bath at 5.03 p.m., in calorimeters at 5.17, out of calorimeters at 5.38. He was perspiring while his hands were in the calorimeters.

TIME	R	L	ROOM	TIME	R	L	ROOM
5.16	32.11	32.07		5.29	32.14	32.180	
5.18	32.09	32.07		5.30	32.15	32.190	24.6
5.19	32.09	32.07		5.31	32.15	32.195	
5.20	32.09	32.08	25.5	5.32	32.16	32.200	24.8
5.21	32.10	32.08		5.33	32.18	32.220	
5.22	32.10	32.08	25.2	5.34	32.20	32.230	24.8
5.24	32.11	32.10	25.1	5.35	32.22	32.250	24.6
5.25	32.11	32.11	24.7	5.36	32.23	32.280	
5.26	32.11	32.12		5.37	32.25	32.300	24.7
5.27	32.12	32.14	24.9	5.38	32.30	32.330	
5.28	32.14	32.16	24.8	5.53	32.16	32.180	

Cooling of calorimeters in 15 minutes, R 0.14°, L 0.15°C. Volume of right hand 344 cc., of left 332 cc. He is right handed. Water equivalent of calorimeters with contents, R 3370, L 3360. Rectal temperature 37.20°C.

Second examination of John Di C., May 26. Pulse 120 at wrist. Hands in bath at 3.31 p.m., in calorimeters at 3.43½, out of calorimeters at 3.58.

TIME	R	L	ROOM	TIME	R	L	ROOM
3.43	31.36	31.32		3.52	31.600	31.560	
3.44	31.36	31.33		3.53	31.630	31.585	24.0
3.45	31.39	31.36	23.4	3.54	31.660	31.620	24.1
3.46	31.42	31.39		3.55	31.700	31.660	
3.47	31.44	31.41		3.56	31.730	31.680	24.1
3.48	31.46	31.43		3.57	31.755	31.700	
3.49	31.49	31.46	23.9	3.58	31.790	31.740	24.0
3.50	31.53	31.49		4.18	31.520	31.470	
3.51	31.57	31.52	23.9				

Cooling of calorimeters in 20 minutes 0.27°C. Volume of right hand 345 cc., of left 342 cc. Water equivalent of calorimeters with contents, R 3371, L 3368. Rectal temperature 37.67°C.

Third examination of John Di C., May 27. Pulse at wrist 92, another count 94, at apex 120. Hands in bath at 3.35 p.m., in calorimeters at 3.45½, out of calorimeters at 4.00.

TIME	R	L	ROOM	TIME	R	L	ROOM
3.45	31.880	31.96		3.54	32.075	32.13	25.1
3.46	31.870	31.94		3.55	32.110	32.17	
3.47	31.880	31.95	24.8	3.56	32.140	32.20	
3.48	31.895	31.97		3.57	32.180	32.23	25.1
3.49	31.920	31.98		3.58	32.220	32.27	
3.50	31.945	32.00	25.0	3.59	32.250	32.30	
3.51	31.970	32.03		4.00	32.290	32.34	
3.52	32.010	32.07	25.0	4.06	32.220	32.27	
3.53	32.045	32.09					

Cooling of calorimeters in 6 minutes 0.07°C. Volume of right hand 352 cc., of left 342 cc. Rectal temperature 37.20°C. Water equivalent of calorimeters with contents, R 3376, L 3368.

Fourth examination of John Di C., June 1. The day was rather warm. Pulse at wrist 60, fairly regular. Hands in bath at 1.58½ p.m., in calorimeters at 2.07½, out of calorimeters at 2.28.

TIME	R	L	ROOM	TIME	R	L	ROOM
2.07	31.540	31.60		2.19	31.800	31.850	26.0
2.08	31.530	31.60		2.20	31.830	31.875	
2.09	31.555	31.62	26.1	2.21	31.860	31.890	
2.10	31.580	31.65		2.22	31.880	31.910	26.1
2.11	31.610	31.68		2.23	31.910	31.940	
2.12	31.640	31.70	26.1	2.24	31.940	31.970	26.1
2.13	31.670	31.72		2.25	31.970	32.000	
2.14	31.690	31.74		2.26	31.995	32.020	
2.15	31.700	31.76	26.1	2.27	32.015	32.050	26.1
2.17	31.740	31.79	26.0	2.28	32.050	32.080	
2.18	31.775	31.82		2.36	31.960	31.990	

Cooling of calorimeters in 8 minutes 0.09°C. Volume of right hand 351 cc., of left 342 cc. Water equivalent of calorimeters with contents, R 3376, L 3368. Pulse (at apex, with stethoscope) 60. Rectal temperature 37.35°C.

Fifth examination of John Di C., June 4. The day was rather cool. Pulse at wrist 70. Hands in bath at 12.27, in calorimeters at 12.36½, out of calorimeters at 12.55.

TIME	R	L	ROOM	TIME	R	L	ROOM
12.36	32.030	32.080		12.47	32.20	32.285	
12.38	32.020	32.090	24.1	12.48	32.22	32.300	
12.39	32.040	32.110		12.49	32.24	32.320	24.10
12.40	32.060	32.130	24.2	12.50	32.25	32.340	
12.41	32.080	32.160		12.51	32.27	32.360	
12.42	32.100	32.180	24.1	12.52	32.29	32.375	
12.43	32.130	32.200		12.53	32.31	32.390	24.00
12.44	32.145	32.230		12.54	32.33	32.410	
12.45	32.160	32.260	24.2	12.55	32.35	32.430	24.05
12.46	32.190	32.275		1.04	32.23	32.310	

Cooling of calorimeters in 9 minutes 0.12°C. Volume of right hand 352 cc., of left 354 cc. Water equivalent of calorimeters with contents, R 3377, L 3379. Rectal temperature 37.02°C.

First examination of Andrew S., May 5. Hands in bath at 2.28 p.m., in calorimeters at 2.39½, out of calorimeters at 2.55.

TIME	R	L	ROOM	TIME	R	L	ROOM
2.39	32.090	32.120		2.48	32.14	32.20	24.0
2.40	32.060	32.090		2.49	32.17	32.22	
2.41	32.060	32.090		2.50	32.20	32.24	23.5
2.42	32.065	32.095	23.5	2.51	32.24	32.28	
2.43	32.070	32.100	23.2	2.52	32.26	32.31	23.6
2.44	32.065	32.110	23.1	2.53	32.29	32.33	
2.45	32.070	32.120	23.3	2.54	32.32	32.37	23.6
2.46	32.090	32.140		2.55	32.35	32.39	
2.47	32.110	32.170	23.8	3.45	31.77	31.77	

Cooling of calorimeters in 50 minutes, R 0.58°, L 0.62°C. Volume of right hand 461 cc., of left hand 465 cc. Water equivalent of calorimeters with contents, R 3464, L 3467. Rectal temperature 37.60°C.

Second examination of Andrew S., May 6. Hands in bath at 2.35 p.m., in calorimeters at 2.47, out of calorimeters at 3.05.

TIME	R	L	ROOM	TIME	R	L	ROOM
2.46	31.710	31.71		2.57	31.90	31.93	
2.48	31.710	31.71		2.58	31.94	31.970	
2.49	31.720	31.73	24.3	2.59	31.97	32.000	24.3
2.50	31.730	31.75	24.3	3.00	32.01	32.400	
2.51	31.740	31.77	24.2	3.01	32.05	32.060	24.1
2.52	31.750	31.79		3.02	32.07	32.080	
2.53	31.770	31.81	24.2	3.03	32.09	32.100	24.1
2.54	31.790	31.83		3.04	31.12	32.135	
2.55	31.830	31.87	24.3	3.05	32.14	32.160	
2.56	31.865	31.90		3.28	31.90	31.880	

Cooling of calorimeters in 23 minutes, R 0.24°, L 0.28°C. Volume of right hand 456 cc., of left hand 477 cc. Water equivalent of calorimeters with contents, R 3460, L 3477. Rectal temperature 37.59°C.

Third examination of Andrew S., May 7. Hands in bath at 3.40 p.m., in calorimeters at 3.50, out of calorimeters at 4.08. Pulse at wrist 96.

TIME	R	L	ROOM	TIME	R	L	ROOM
3.49	31.85	31.78		4.00	32.15	32.095	
3.51	31.85	31.78	24.7	4.01	32.18	32.120	24.5
3.52	31.87	31.80		4.02	32.23	32.180	
3.53	31.87	31.82		4.03	32.26	32.210	24.4
3.54	31.89	31.85	24.8	4.04	32.29	32.250	
3.55	31.93	31.89		4.05	32.34	32.290	24.5
3.56	31.98	31.93		4.06	32.37	32.320	
3.57	32.01	31.98	24.9	4.07	32.42	32.360	
3.58	32.07	32.01		4.08	32.46	32.400	
3.59	32.10	32.05	24.9	4.17	32.36	32.29	

Cooling of calorimeters in 9 minutes, R 0.10°C., L 0.11°C. Volume of right hand 467 cc., of left hand 480 cc. Water equivalent of calorimeters with contents, R 3469, L 3479. Rectal temperature 37.50°C.

Fourth examination of Andrew S., May 8. Weather colder than at last examination. Hands in bath at 11.20 a.m., in calorimeters at 11.30, out of calorimeters at 11.50.

TIME	R	L	ROOM	TIME	R	L	ROOM
11.29½	31.780	31.790		11.41	32.02	32.05	
11.31	31.790	31.795		11.42	32.05	32.08	24.1
11.32	31.795	31.805	24.1	11.43	32.08	32.11	
11.33	31.800	31.820		11.44	32.12	32.15	
11.34	31.810	31.850	24.0	11.45	32.15	32.19	24.1
11.35	31.840	31.880	24.0	11.46	32.18	32.21	
11.36	31.870	31.900		11.47	32.22	32.26	
11.37	31.900	31.930		11.48	32.26	32.29	24.1
11.38	31.930	31.960	24.3	11.49	32.29	32.32	
11.39	31.960	31.990		11.50	32.32	32.35	24.1
11.40	31.990	32.020	24.3	12.02	32.17	32.10	

Cooling of calorimeters in 12 minutes 0.15°C. Volume of right hand 471 cc., of left 463 cc. Water equivalent of calorimeters with contents, R 3472, L 3465. Pulse at apex 98. Rectal temperature 37.36°C.

Fifth examination of Andrew S., May 10. Hands in bath at 2.29 p.m., in calorimeters at 2.39½, out of calorimeters 2.55.

TIME	R	L	ROOM	TIME	R	L	ROOM
2.39	31.970	32.00		2.49	32.42	32.44	
2.41	32.020	32.05		2.50	32.47	32.49	
2.42	32.060	32.09		2.51	32.515	32.53	25.0
2.43	32.100	32.14	24.9	2.52	32.56	32.58	25.2
2.44	32.160	32.19		2.53	32.60	32.62	
2.45	32.200	32.23	24.8	2.54	32.65	32.67	25.1
2.46	32.265	32.29		2.55	32.70	32.70	
2.47	32.310	32.33	24.7	3.17	32.46	32.46	
2.48	32.370	32.39	24.9				

Cooling of calorimeters in 22 minutes 0.24°C. Volume of right hand 462 cc., of left 462 cc. Water equivalent of calorimeters with contents, R 3465, L 3465. Pulse 80 at wrist, 82 at apex. The strong pulse beats have a greater amplitude than at any of the previous examinations. Rectal temperature 37.75°C.

Sixth examination of Andrew S., May 12. Hands in bath at 2.50 p.m., in calorimeters at 3.02, out of calorimeters at 3.19. Pulse 76 (at wrist).

TIME	R	L	ROOM	TIME	R	L	ROOM
3.01	31.88	31.93		3.12	32.20	32.28	26.1
3.03	31.89	31.97	26.1	3.13	32.24	32.31	
3.04	31.92	31.99	26.5	3.14	32.29	32.35	26.2
3.05	31.94	32.01		3.15	32.33	32.38	
3.06	31.97	32.04	26.3	3.16	32.36	32.41	
3.07	31.99	32.08		3.17	32.29	32.44	26.3
3.08	32.04	32.12	26.2	3.18	32.43	32.48	26.3
3.09	32.08	32.17		3.19	32.48	32.51	26.1
3.10	32.12	32.20	26.2	3.30	32.36	32.49	
3.11	32.16	32.24					

Cooling of calorimeters in 11 minutes 0.12°C. Volume of right hand 452 cc., of left 457 cc. Water equivalent of calorimeters with contents, R 3456, L 3460. Rectal temperature 37.57°C.

First bloodflow examination of E. P. W., February 19. Hands in bath at 3.03 p.m., in calorimeters at 3.14, out of calorimeters at 3.30.

TIME	R	L	ROOM	TIME	R	L	ROOM
3.16	31.50	31.47		3.24	31.595	31.57	
3.17	31.52	31.48	19.2	3.25	31.60	31.585	20.0
3.18	31.525	31.49		3.26	31.61	31.60	
3.19	31.53	31.49		3.27	31.63	31.63	20.0
3.20	31.54	31.50	20.0	3.38	31.66	31.65	
3.21	31.56	31.52		3.29	31.67	31.66	
3.22	31.57	31.54	20.0	3.30	31.69	31.67	
3.23	31.58	31.56		3.42	31.45	31.44	

Cooling of calorimeters in 12 minutes, R 0.24°, L 0.23°C. Pulse 100. Volume of right hand 387 cc., of left 356 cc. Water equivalent of calorimeters with contents, R 3405, L 3380. Mouth temperature 36.35°C.

Second examination of E. P. W., February 20. Hands in bath at 3.44 p.m., in calorimeters at 3.55, out of calorimeters at 4.12.

TIME	R	L	ROOM	TIME	R	L	ROOM
3.57	31.19	31.36		4.06	31.51	31.655	19.9
3.58	31.22	31.42		4.07	31.56	31.670	
3.59	31.26	31.45	19.6	4.08	31.59	31.69	19.9
4.00	31.29	31.47		4.09	31.65	31.74	
4.01	31.33	31.50	19.7	4.10	31.68	31.76	20.0
4.02	31.36	31.53		4.11	31.72	31.79	
4.03	31.39	31.55	19.7	4.12	31.76	31.80	19.9
4.04	31.42	31.57		4.28	31.47	31.50	
4.05	31.495*	31.64*					

* Reading verified.

Cooling of calorimeters in 16 minutes, R 0.29°, L 0.30°C. Pulse 92 (amplitude considerably greater than at first examination). Mouth temperature 36.35°, rectal temperature 36.63°C. Volume of right hand 394 cc., of left 344 cc. Water equivalent of calorimeters with contents, R 3410, L 3370.

Third examination of E. P. W., February 24. Hands in bath at 3.00 p.m., in calorimeters at 3.11, out of calorimeters at 3.25.

TIME	R	L	ROOM	TIME	R	L	ROOM
3.13	32.09	32.29		3.20	32.26	32.44	
3.14	32.11	32.32	17.3	3.21	32.27	32.45	17.5
3.15	32.13	32.34		3.22	32.28	32.46	
3.16	32.16	32.36	17.4	3.23	32.30	32.465	17.5
3.17	32.17	32.37	17.5	3.34	32.31	32.47	
3.18	32.20	32.39		3.25	32.31	32.47	
3.19	32.23	32.42		3.39	32.00	32.14	

Cooling of calorimeters in 14 minutes, R 0.31°, L 0.33°C. Pulse 62. Rectal temperature 37.13°C. Volume of right hand 369 cc., of left 346 cc. Water equivalent of calorimeters with contents, R 3390, L 3372.

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STUDIES ON THE CIRCULATION IN MAN

XV. FURTHER OBSERVATIONS, CHIEFLY PHARMACOLOGICAL, ON THE CRITERIA BY WHICH DEFICIENCIES IN THE BLOODFLOW (IN THE HANDS OR FEET) DUE TO MECHANICAL CAUSES MAY BE DISCRIMINATED FROM CHANGES DUE TO FUNCTIONAL (VASOMOTOR) CAUSES

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In Paper XIII of this series[1] I have investigated certain criteria by which a deficiency in the bloodflow through the hands or feet, or through one hand or foot, due to mechanical causes (embolism, compression or ligation of arteries) is distinguished from a deficiency due to vasoconstriction. One of these criteria is the constancy of the ratio of the flow in a mechanically obstructed part to the flow in a normal part in the same individual in successive measurements made at not too long intervals and under approximately the same external conditions, especially the same external temperature. Another is the relatively small response of the flow in the mechanically obstructed part to conditions which cause general cutaneous vasodilatation, especially a considerable increase in the external temperature. A third criterion investigated is the relatively feeble vasomotor reflex in the mechanically obstructed part when the contralateral part is immersed in warm or cold water. None of these criteria holds good for a deficient flow due to a functional (vasomotor) cause. The ratio of the flow in a part which happens at one time to have a deficient

[1] Journal of Experimental Medicine, 1915, xxii, No. 1.

circulation owing to increased vasoconstriction to the flow in a part in the same person with normal circulation does not remain constant from day to day. The ratio is easily altered when the external temperature is changed, and the flow in the affected part is readily influenced reflexly from the contralateral part. In this paper I desire to supplement these observations, in particular by observations in which the stability of the flow in the part in which it was deficient was tested under the administration of drugs causing vasodilatation (nitroglycerine, alcohol). It is clear that such drugs might be expected to affect the flow in a part with mechanically obstructed circulation to a smaller extent than the flow in a part whose circulation was diminished by vasoconstriction. The conclusion was verified in a number of cases.

John G.,[2] a Polish laborer, aged 41 years, came under observation for examination of the bloodflow at Lakeside Hospital on March 25, 1915. He had had his left leg amputated in the middle of the lower leg in July, 1909, and his right leg amputated at the middle of the thigh in May, 1913, for thrombo-angitis obliterans. He complains of pain in the hands, especially the left. The terminal phalanx of the left middle finger shows a gangrenous area at the tip and around the foot of the nail, which has existed for six weeks. There is discoloration, but the skin is unbroken as yet. There is no history of injury. The brachial pulse is well felt in the left arm, but the radial not. The patient says no pulse has been felt at his left wrist since it was fractured a while ago. The right radial pulse is good.

The bloodflow on March 25, 1915, was 10.32 gm. per 100 cc. per minute in the right hand and 8.6 gm. in the left, with room temperature 22.0°C. before the testing of the vasomotor reaction. During immersion of the right hand in cold water the flow in the left was only diminished to 7.90 gm. per 100 cc. per minute for the whole period of immersion of 9 minutes. During a 10 minutes immersion of the right hand in warm water the flow in the left was increased only to 8.08 gm. per 100 cc. per minute. That is to say, there were practically no vasomotor reflexes in the left hand from the contralateral hand, indicating a high degree of immobility of the vessel walls.

On April 27, 1915, the bloodflow in the hands was again examined

[2] I am indebted to my colleague, Dr. G. W. Crile, for the opportunity of studying this case.

with a very much higher room temperature. The gangrenous region on the terminal phalanx of the left middle finger had increased in area and depth. There was some pain in the hand from time to time but no pain in the necrosed area. The points of the little and ring fingers of the left hand, as well as the point of the middle finger were painful now.

The flow in the right hand was 11.29 gm. per 100 cc. per minute for 9 minutes before the vasomotor reflexes were tested, in the left only 5.64 gm., with room temperature 28.5°C. The diminution in the blood in the left hand as compared with the first examination, notwithstanding the high external temperature, is definite proof of the marked deterioration of the circulation in that hand in the interval. The great deficiency in the left hand as compared with the right in the face of the high temperature is conclusive evidence of mechanical obstruction. The vasomotor reflexes from the contralateral hand were again practically absent, or at any rate without influence on the bloodflow.

On April 30 the influence of nitroglycerine on the hand flow was tested. The day was cold, but it is quite characteristic of such conditions that the flow in the left hand was almost as great as on April 27 when the weather was warm (5.31 gm. per 100 cc. per minute for 7 minutes before the administration of nitroglycerine); whereas the flow in the right hand was diminished to 8.28 gm. per 100 cc. per minute (ratio of flow in left hand to that in right 1:1.559) with room temperature 23.4°C. For the first 4 minutes after the administration of nitroglycerine had begun, the flow in the right hand was 8.45 gm. per 100 cc. per minute as compared with 5.74 gm. in the left hand (ratio 1:1.472). For the next 12 minutes with further administration of nitroglycerine the flow in the left hand remained at 5.8 gm., while that in the right increased to 9.36 gm. per 100 cc. per minute (ratio 1:1.613). The change in the ratio shows that the vasodilatation has affected the right hand more than the left. Nausea now came on. The patient felt sick and his face became markedly pale for 3 minutes. During this period the flow in the right hand fell to 4.46 gm. and that in the left hand to 4.07 gm. per 100 cc. per minute (ratio 1: 1.09). The great change in the ratio shows clearly that the diminution in the hand flows was not due mainly to a central cause (inhibition of the heart), or to a vasomotor effect produced elsewhere than in the extremities (e.g., in the splanchnic area), but to a peripheral vasoconstriction naturally affecting the right hand with its relatively mobile vessels far more than the left hand.[3]

[3] Stewart: Jour. Pharmacol. and Exper. Therap., 1911, ii, 481.

With the recovery from nausea the pallor of the face disappeared, and the flow in the right hand increased far more than that in the left (to 8.26 gm. per 100 cc. per minute for the right hand as compared with 4.32 gm. for the left for the last 10 minutes of the experiment, ratio 1:1.91).

The great relative increase in the flow in the right hand in the last 10 minutes of the experiment as compared with the left hand indicates the passing off of the vasoconstriction associated with the period of nausea. The left hand owing to the anatomical changes in the vessels is naturally but little affected. The flow in the left hand does not return to its initial value either because the driving power of the heart is still reduced or because a general vasodilatation still keeps the blood pressure lower than at first. If the blood pressure is lowered and the mechanical conditions do not permit appreciable diminution of the total vascular resistance in the left hand, the flow in that hand must be diminished, while the flow in the normal or approximately normal right hand may even be increased.

The effect of alcohol (or rather of certain alcoholic beverages) on the hand flow was first studied in a normal man (M. C.), 26 years of age. He had on many previous occasions been used as a subject, so that the limits of range of his hand flow were known.

For 10 minutes before the administration of alcohol, the flow was 14.74 gm. per 100 cc. per minute for the right hand and 13.58 gm. for the left (ratio 1:1.08) with room temperature 23.2°C. The first effect of alcohol (in the form of port wine) was to diminish the flow in both hands. This initial diminution has also been seen in the other cases. The flow for the first 10 minutes after the administration of the wine was begun was 12.81 gm. per 100 cc. per minute for the right hand and 11.18 gm. for the left hand (ratio 1:1.14). The diminution was not the same in the two hands, being proportionally greater in the left, and therefore it could not have been due solely to an action on the heart or to a vasomotor effect elsewhere than in the extremities. It must have been due partly at least to a vasoconstriction in the hands, and there is no obvious reason to expect that such a vasoconstriction should be exactly the same on the two sides. The initial effect of the alcohol is very promptly

manifested, certainly within the first minute. This is true of whisky as well as wine. It would therefore seem probable that it depends upon a vasomotor reflex liberated from the mucous membrane of the mouth, oesophagus or stomach. The same result was seen in another man in normal health but exhibiting a peculiarity in the hand flow which will be mentioned in the proper place. Neither of the subjects was an habitual drinker. The wine was relished by both, but the whisky, diluted with an equal volume of water, was not so well liked. In a patient with cardiorenal disease whisky also caused a diminution in the hand flow for the first 10 minutes after its administration. The whisky was not well liked in this case either. This is mentioned because the handflow is very easily influenced by psychical events, disgust, fear or painful impressions causing a prompt and decided diminution. But the fact that the wine caused a similar effect, although it was relished, makes it probable that in the case of the whisky also it is the reflex vasomotor effect and not a psychical reaction which is responsible for the initial vasoconstriction.

The next effect of the alcoholic beverage on the hand flow is an increased circulation in both hands. In M. C. for the second 10 minutes of the alcohol period the flow in the right hand was 16.77 gm. per 100 cc. per minute and in the left hand 15.76 gm. (ratio 1:1.06). For the next 7 minutes of the alcohol period, the flows were still further increased to 18.32 gm. and 17.61 gm. per 100 cc. per minute for the right and left hand respectively (ratio 1:1.04). The decline in the ratio shows that the initial moderate difference in flow in the two hands becomes continuously less as the absolute value of the flows increases. This could not be due to central changes alone or to vasomotor changes in other regions affecting both hands indirectly and therefore equally. It follows that some portion of the increased flow in the hands must be due to vasodilatation in the hands themselves. It is obvious that if the initial vasoconstriction was somewhat greater in the left hand than in the right, as vasodilatation under the influence of the alcohol increased, this difference would tend to disappear.

An interesting point well brought out in this experiment, and also observed in others, is that alcohol favors reflex vasodilatation in the hands. Thus, 27 minutes after the administration of alcohol was commenced the left hand was immersed in warm water. The initial diminution of the flow in the right hand, which is normally seen, was very slight and transient (from 18.32 gm. to 17.81 gm. per 100 cc. per minute for the first 3 minutes of immersion of the left hand in the warm water). Then followed a marked increase in the flow, which despite its previous high level rose to 23.57 gm., much the largest flow seen in M. C. on the twenty or more occasions on which his hand flow was measured in the past four years. This observation suggests that one way in which alcohol produces dilatation of cutaneous vessels is by so altering the response of the vasomotor centres to reflex stimuli that vasodilatation is favored. How far "paralysis" of vaso-constrictor tone by a direct depressant action on the vasomotor centres is a factor is not indicated by our observations.

The other normal, or at least healthy man (John R., 22 years old), in whom the effect of alcohol on the hand flow was investigated presents the peculiarity, not hitherto observed in any other healthy person, that the flow in the left hand is permanently very decidedly smaller than in the right. This has been the case in tests made over a period of more than two years. The ratio of the flows in the two hands remains so stable as to suggest a mechanical cause for the difference, for example a congenital difference in cross section of the two subclavians. The suggestion that a mechanical and not a vasomotor factor underlies the difference in flow is strengthened by the fact that conditions which cause considerable variations in the absolute amount of the hand flow do not tend to equalize the flow in the two hands.[4] This idea is supported by the alcohol observations. For the 10 minutes before the administration of strong port wine, the flow in the right hand was 18.52 gm. per 100 cc. per minute, and that in the left hand 14.01 gm. (ratio 1:1.32), with room temperature 25.0°C.

[4] Journal of Experimental Medicine, 1915, xxii, No. 1.

For the first two minutes after the taking of wine was begun the flow in both hands was diminished, the diminution being proportionally much greater in the right hand than in the left, so that the flow became about equal in the two hands.[5] The fact that the diminution was so much greater in the right hand shows that it must have been due at least partly to vasoconstriction affecting the hands, although a temporary decrease in the output of the heart is not excluded. Just as in the case of John G. during the period of nausea, the vasoconstriction would necessarily tend to equalize the flow in the two hands if the flow in one were already diminished by a mechanical cause. Of course the same would be true if the vasoconstrictor tone of one hand was already greater than that of the other at the time the fresh vasoconstriction occurred. But we know that this is not the explanation in the case of John G., and that it is not the explanation in the case of John R. is indicated by the fact that for the next 8 minutes of the alcohol period when vasodilatation was already marked, a decided inequality in the two hand flows had already returned, the flow in the right being 19.56 gm. per 100 cc. per minute and that in the left 15.87 (ratio 1:1.23). For the next 10 minutes the flows were 20.70 and 16.14 gm. per 100 cc. per minute for the right and left hands respectively (ratio 1:1.28) and for the remaining 14 minutes of the experiment 21.99 gm. per 100 cc. per minute for the right hand against 17.07 gm. for the left (ratio 1:1.29, approximately the same as before the administration of alcohol.) These flows are also absolutely the largest ever observed in this individual.

The initial diminution in the hand flow after alcohol was also seen in Otis S., a man suffering from cardiorenal disease(chronic interstitial nephritis and myocarditis), with liquid in the right pleural cavity and the abdominal cavity and oedema of the arms, hands, legs and feet. About an hour after the aspiration of 2 litres of liquid from the right thorax, an examination of the flow

[5] It must be pointed out that too much stress must not be laid on the apparent equality of the flows here because the error in calculating the flow for so short a period as two minutes would be 10 per cent if an error of 0.01°C. were made in a thermometer reading.

in the hands was made, during the course of which the patient was given 2 ounces of whisky followed by some water. He said he did not like the whisky and its administration was followed by flatulence. The observations were only continued for 10 minutes after the whisky was given. The flow in the right hand for the 9 minutes preceding the giving of alcohol was 6.83 (7.98)[6] per 100 cc. per minute, and that in the left hand 7.94 (9.11) gm. (ratio 1:1.14) with the very high room temperature 29.8°C. For the 10 minutes after the alcohol was given the flows were 5.93 (6.92) gm. and 6.40 (7.34) gm. per 100 cc. per minute for the right and left hands respectively (ratio 1:1.06). For the first minute of the alcohol period the flows were much more decidedly diminished, to 4.2 (4.9) gm. for the right hand and 4.1 (4.6) gm. for the left.

SUMMARY

1. To the criteria already described which can be employed to discriminate between deficiency in the bloodflow (in the hands or feet) due to mechanical causes and deficiency due to vasomotor action, may be added the behavior of the flow when drugs which cause vasodilatation (nitroglycerine, alcohol) are administered.

2. Alcoholic beverages (wine, whisky) cause first a diminution and then an increase in the hand flow.

PROTOCOLS

First bloodflow examination of John G., March 25, 1915. Hands in bath at 2.42 p.m., in calorimeters at 2.52½. At 3.05 right hand put into water at 8.2°C.; at 3.14 into water at 43.7°C. At 3.24 left hand removed from calorimeter.

[6] The numbers in parentheses are the flows calculated on the true volume of the hand tissue after deducting the oedema fluid. The true volume was obtained by measurements made when the hands were free from oedema.

TIME	TEMP. OF CALORIMS		ROOM	TIME	TEMP. OF LEFT CALO-RIM	ROOM	TIME	TEMP. OF LEFT CALORIM	ROOM
	Right	Left							
2.52	32.220	32.190		3.06	32.66	22.1	3.19	33.04	22.2
2.54	32.270	32.240	21.8	3.07	32.69		3.20	33.06	
2.55	32.310	32.270	22.0	3.08	32.74	22.0	3.21	33.09	22.15
2.56	32.360	32.320	21.9	3.09	32.755	21.9	3.22	33.12	22.2
2.57	32.400	32.360		3.10	32.785		3.23	33.15	22.2
2.58	32.450	32.400	21.9	3.11	32.81	22.0	3.24	33.17	
2.59	32.500	32.450	21.9	3.12	32.84				
3.00	32.550	32.480	21.9	3.13	32.87	22.0	3.37	32.96	
3.01	32.590	32.520	22.0	3.14	32.905		3.37	(Rt. 32.23)	
3.02	32.630	32.550	22.0	3.15	32.94	22.15			
3.03	32.680	32.580	22.0	3.16	32.96				
3.04	32.720	32.610	22.0	3.17	32.98	22.2			
3.05	32.770	32.645		3.18	33.01	22.2			

Cooling of calorimeters, right 0.54° in 32 minutes, left 0.21° in 13 minutes. Pulse 84. Volume of right hand 522 cc., of left 513 cc. Rectal temperature 37.53°. Water equivalent of calorimeters with contents, R 3512, L 3505.

Second bloodflow examination of John G., April 27, 1915. Hands in bath at 2.09 p.m., in calorimeters at 2.21. At 2.32 right put into water at 9.5°C., and at 2.39 into water at 44.1°C. At 2.47 left hand removed from calorimeter.

TIME	R	L	ROOM	TIME	R	L	ROOM
2.20........	32.00	31.95		2.36		32.410	
2.22........	32.07	32.00	28.4	2.37		32.440	28.4
2.23........	32.12	32.03		2.38		32.460	
2.24........	32.20	32.06	28.5	2.39		32.485	
2.25........	32.27	32.10		2.40		32.510	28.6
2.26........	32.33	32.13	28.5	2.41		32.530	
2.27........	32.39	32.16		2.42		32.550	28.8
2.28........	32.45	32.19	28.7	2.43		32.575	
2.29........	32.52	32.22		2.44		32.600	
2.30........	32.58	32.25	28.7	2.45		32.625	29.0
2.31........	32.62	32.27		2.46		32.650	
2.32........	32.69	32.29		2.47		32.670	
2.33........		32.32	28.5	2.48	32.56		
2.34........		32.35		3.01	32.46	32.560	
2.35........		32.38	28.5				

Cooling of calorimeters R, 0.10° in 13 minutes, L 0.11° in 14 minutes Volume of right hand 549 cc., of left 527 cc. Water equivalent of calorimeters with contents R 3534, L 3516. Rectal temperature 37.45°C. Blood pressure, right arm 185, 100 (sound gone).

Third bloodflow examination of John G., April 30, 1915. From time to time during the examination nitroglycerine (Spiritus Glonoini) was administered on the tongue. Hands in bath at 2.10½ p.m., in calorimeters at 2.20½, out of calorimeters at 2.58. Pulse 96.

TIME	R	L	ROOM	NOTES	TIME	R	L	ROOM	NOTES
2.20	31.79	31.840			2.40	32.58	32.27		
2.21	31.79	31.830			2.41	32.63	32.29	23.7	
2.22	31.85	31.860	23.2		2.42	32.67	32.31		
2.23	31.89	31.885	23.3		2.43	32.71	32.33	23.7	
2.24	31.95	31.910			2.44	32.74	32.35	23.7	Face getting pale.
2.25	31.995	31.930	23.4		2.45	32.79	32.36		Face pale. Yawns. Nausea.
2.26	32.035	31.950			2.46	32.80	32.37		
2.27	32.080	31.970	23.5		2.47	32.81	32.38		Feels sick, but does not want to vomit.
2.28	32.115	31.990	23.5	Pulse 102	2.48	32.82	32.39		Pulse 85. Volume of carotid pulse much reduced.
2.29	32.14	32.010		2 drops Sp. Gl.	2.49	32.86	32.41		He says he is now all right. Tongue and lips pale.
2.30	32.18	32.030	23.5		2.50	32.88	32.42		
2.31	32.22	32.050	23.5		2.51	32.90	32.43	23.8	Yawns. Some noise in ears.
2.32	32.270	32.080		Pulse not increased	2.52	32.93	32.44		Pulse 80. Sweats on face.
2.33	32.30	32.100	23.5	3 drops Sp. Gl.	2.53	32.97	32.45		Not so pale now.
2.34	32.35	32.130	23.5	No flushing of face	2.54	33.00	32.46	23.7	Pulse 88; volume much better.
2.35	32.395	32.150		Head a little sore but no throbbing	2.55	33.03	32.475		
2.36	32.42	32.180	23.6		2.56	33.07	32.48		Feels back cold.
2.37	32.46	32.200	23.6		2.57	33.09	32.49	23.9	
2.38	32.50	32.230		5 drops Sp. Gl.	2.58	33.11	32.50		
2.39	32.54	32.250	23.7		3.07	32.97	32.37		Pulse 89

Cooling of calorimeters, R 0.14°, L 0.13° in 9 minutes. Volume of right hand 544 cc., of left 521 cc. Rectal temperature 37.35°C. Water equivalent of calorimeters with contents, R 3530, L 3512.

Examination of bloodflow in M. C. to test influence of alcohol. Hands in bath at 3.18 p.m., in calorimeters at 3.28. Pulse at beginning of observations 94. At 3.40, 70 cc. port wine given; at 3.41, 70 cc. more; at 3.44, an additional 70 cc. At 3.49½ p.m., he got 25 cc. whisky diluted with an equal volume of water. "It takes his breath."

TIME	R	L	ROOM	TIME	R	L	ROOM	NOTES
3.27	31.90	31.88		3.53	33.320	33.080	23.3	
3.29	31.98	31.86	23.2	3.54	33.380	33.150		Head heavy, feels sleepy and tired.
3.30	32.06	31.95		3.55	33.430	33.190		Pulse 88.
3.31	32.11	32.04		3.57	33.530	33.300		
3.32	32.19	32.09		2.58	33.590	33.350		
3.33	32.27	32.15		3.59	33.630	33.400		
3.34	32.33	32.21	23.2	4.00	33.690	33.450	23.3	
3.35	32.40	32.26		4.01	33.740	33.510		
3.36	32.47	32.32		4.02	33.790	33.555	23.5	
3.37	32.53	32.38	23.2	4.03	33.840	33.600		Head dizzy.
3.38	32.61	32.45		4.04	33.890	33.650		
3.39	32.68	32.50	23.2	4.05	33.940	33.750		
3.40	32.72	32.55		4.06	33.980	33.750		
3.41	32.77	32.57		4.07	34.020	33.790		Left hand put in water at 43.5° C.
3.42	32.79	32.60		4.08	34.060		23.4	
3.43	32.84	32.64		4.09	34.095			
3.44	32.89	32.68		4.10	34.140			
3.45	32.91	32.70		4.11	34.190		23.3	
3.46	32.96	32.75	23.2	4.12	34.240			
3.47	33.00	32.78		4.13	34.290		23.2	Feels sleepy and warm.
3.48	33.07	32.84		4.14	34.340			
3.49	33.11	32.88		4.15	34.390			
3.50*	33.17	32.94	23.3	4.16	34.430			Feels effect of alcohol decidedly.
3.51	33.21	32.97		4.17	34.490		23.3	Hand removed from calorimeter.
3.52	33.27	33.04		4.25	34.350	33.50		

* At this point he says he feels warm all over. Before this he only felt warm "inside."

Cooling of calorimeters, R 0.14°C. in 8 minutes, L 0.29°C. in 18 minutes. Volume of right hand 512 cc., of left 495 cc. Water equivalent of calorimeters with contents, R 3505, L 3491. Rectal temperature 37.00°C. At the end of the experiment he walked quite straight along a crack. Later the dizziness went on increasing and he still felt it after two hours.

John R. Examination of effect of alcohol upon the bloodflow. Hands in bath at 1.25 p.m., in calorimeters at 1.35, out of calorimeters

at 2.21. Pulse at beginning of observation 60, in two observations. The day was muggy. At 1.47 p.m., he got 70 cc. of port wine; at 1.51, 35 cc.; at 1.58 p.m., 70 cc. more. At 2.09, he got 20 cc. of whisky diluted with an equal volume of water. He did not like the whisky as well as the wine. He said it tasted bad.

TIME	R	L	ROOM	TIME	R	L	ROOM	NOTES
1.34½	31.700	31.690		1.59	33.10	32.740	25.1	Feels warm "inside."
1.36	31.720	31.720	24.7	2.00	33.17	32.770		Slightly dizzy.
1.37	31.790	31.750	24.9	2.01	33.23	32.830	25.1	
1.38	31.860	31.800		2.02	33.29	32.870		
1.39	31.925	31.855	25.1	2.03	33.35	32.920		Pulse 68.
1.40	32.000	31.900		2.04	33.40	32.970		
1.41	32.070	31.950	25.15	2.05	33.43	32.990		Dizziness increasing.
1.42	32.130	32.000	25.1	2.06	33.48	33.030	25.0	
1.43	32.210	32.050		2.07	33.51	33.060		
1.44	32.270	32.080	25.0	2.08	33.56	33.100		
1.45	32.320	32.110		2.09	33.60	33.140		
1.46	32.380	32.160	24.8	2.10	33.63	33.155	25.1	
1.47	32.460	32.210		2.11	33.67	33.190		Sleepy; increasing dizziness.
1.48	32.485	32.240		2.12	33.73	33.240		
1.49	32.530	32.280		2.13	33.78	33.285	25.1	Pulse 69.
1.50	32.610	32.340	24.9	2.14	33.82	33.340		Dizziness increasing.
1.51	32.690	32.390		2.16	33.90	33.410		
1.52	32.720	32.430	25.0	2.17	33.94	33.440	25.0	
1.53	32.780	32.460		2.18	33.98	33.460		
1.54	32.830	32.520		2.19	34.02	33.490	25.0	Dizziness constantly increasing. No other effect
1.55	32.880	32.555	24.9	2.20	34.06	33.525		
1.56	32.950	32.600	24.9	2.21	34.09	33.550		
1.57	33.000	32.655		2.27	34.00	33.460		Walks straight on floor.
1.58	33.060	32.690						

Cooling of calorimeters in 6 minutes 0.09°C. Volume of right hand 410 cc., of left 383 cc. Water equivalent of calorimeters with contents, R 3423, L 3391. Pulse 54. Rectal temperature 36.65°C.

Otis S. Hands in bath at 3.01 p.m., in calorimeters at 3.10¼, out of calorimeters at 3.31. At 3.21 he received ℥ii of whisky and then a glass of water.

TIME	R	L	ROOM	TIME	R	L	ROOM
3.09	31.730	31.700	29.45	3.22	32.235	32.350	29.8
3.12	31.800	31.820	29.90	3.23	32.270	32.390	
3.13	31.840	31.860		3.24	32.300	32.430	
3.14	31.895	31.920	29.80	3.25	32.340	32.470	29.8
3.15	31.950	31.980		3.26	32.380	32.510	
3.16	32.000	32.040	29.90	3.27	32.415	32.545	
3.17	32.060	32.120		3.28	32.455	32.590	
3.18	32.090	32.160		3.29	32.495	32.630	
3.19	32.130	32.210	29.80	3.30	32.520	32.660	29.9
3.20	32.170	32.260		3.31	32.570	32.725	
3.21	32.210	32.325		3.39	32.510	32.835	

Cooling of calorimeters 0.06 in 8 minutes. Rectal temperature 37.8°. Volume of right hand in calorimeter 543 cc., of left hand 570 cc. Water equivalent of calorimeters with contents, R 3429, L 3451.

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STUDIES ON THE CIRCULATION IN MAN.

XVI. A STUDY OF THE DEVELOPMENT OF THE COLLATERAL CIRCULATION IN THE RIGHT HAND AFTER LIGATION OF THE INNOMINATE ARTERY FOR SUBCLAVIAN ANEURYSM.

BY G. N. STEWART, M.D.

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Through the kindness of my colleague, Dr. Carl A. Hamann, I have been enabled to study two cases in which he successfully ligated the innominate and common carotid arteries for subclavian aneurysm. I have employed the method of measuring the blood flow in the hands previously described by me.[1]

The results in the first case, that of Mrs. K., 68 years of age, have already been published,[2] and need only be briefly alluded to here for comparison with the second case. I did not have the opportunity of examining the blood flow before the operation on Mrs. K. The operation was performed on Feb. 26, 1913. On Mar. 20, the flow in the right hand was 1.50 gm. per 100 cc. of hand per minute, and in the left 5.32 gm. (ratio 1 : 3.54), with room temperature 26.7° C. On Mar. 21 the flows were 1.83 gm. and 6.38 gm. for the right and left hands, respectively (ratio 1 : 3.48), with room temperature 22.7° C. On July 9, 1913 (19 weeks after the operation), the flow in the right hand was 8.26 gm. per 100 cc. per minute and in the left 10.69 gm. (ratio 1 : 1.3), with room temperature 26.2° C. There was no pulse in the accessible arteries of the right arm. Yet it is obvious from the blood flow measurements that a very satisfactory collateral circulation had been established. At the present time the patient is still alive, and a pulse has returned.

The second case was that of a colored man, Arthur B., aged 25 years, height 5 feet, 4 inches, weight 132 pounds. He was admitted to the City Hospital May 6, 1915, complaining of pain in the right shoulder and right arm. The pain began 3 weeks before he applied for admission coincidently with the appearance of a small lump below the right clavicle, which rapidly increased in size. The pain and muscular weakness in the right arm soon forced him to quit work. On admission the loss of power in the right forearm and hand was marked; in the upper arm and shoulder it was less marked, though evident. There is no atrophy

[1] Stewart, G. N., *Heart*, 1911, iii, 33.

[2] Stewart, *Arch. Int. Med.*, 1914, xiii, 1.

or edema of the right arm. The circumference of the right arm at the middle of the biceps is 30 cm., of the left 27 cm. The circumference of the right forearm is 28½ cm., of the left 27 cm. The man is right handed. The left radial pulse is of greater volume than the right. The pulse in the two radials is synchronous. Blood pressure in right arm, systolic 110, diastolic 88; in left arm, systolic 130, diastolic 70. The fingers of the right hand are markedly clubbed.

May 11, 1915. Blood: leucocytes 11,600, hemoglobin 80 per cent. Wassermann + + +.

On May 11 the innominate and common carotid arteries were ligated.

May 19, 1915. He is fairly well. The right hand is not cold. He has no pain in the right arm, but the arm and hand feel tired. The radial side of the palm of the hand feels numb. There is no pulse at the left wrist. Pulse rate 116 (sitting). The blood flow in the hands was measured May 8, that is, 3 days before the operation, and again on May 22, 11 days after the operation. Further examinations were made on May 28, June 4, and June 11.

The patient's friends prevailed on him to leave the hospital on May 24, and he subsequently returned from time to time for the blood flow examinations.

On May 8 the flow in the right hand was 12.52 grams per 100 cc. of hand per minute for the last nine minutes in the calorimeters, and that in the left hand 6.36 grams, with average room temperature of 22.5° C. It may appear puzzling at first thought that the flow in the right hand should be double that in the left, while the amplitude of the right radial pulse is so much smaller than that of the left. The pulse as felt by the finger, however, is only a rough criterion of the blood flow on the assumption that the anatomical conditions are normal. In the present case the pulse wave must be supposed to be greatly diminished and its form distorted in passing through the aneurysm, but that is no reason for expecting that the mass movement of the blood should be diminished as well. The systolic pressure in the right arm was 110, the diastolic 88 mm. of mercury. The pulse pressure, which can alone be detected by the finger, is only 22 mm. of mercury. In the left arm the systolic pressure was 130, the diastolic 70, and the pulse pressure 60 mm. of mercury. But while this makes it clear that there is no ground for expecting a smaller flow on the side of the smaller pulse, why should the flow be so much larger on that side? The explanation is probably twofold: first, there is evidence of pressure on constituents of the brachial plexus supplying the right hand. Now pressure sufficient to cause loss of power in the skeletal muscles may be assumed to cause also some loss of vasomotor tone, since the vasomotor

fibers in the brachial plexus cannot conceivably be protected from the pressure. A loss of vasomotor tone in a hand will of course be accompanied by an increased blood flow. As a matter of fact, I have found that in early unilateral brachial neuritis the blood flow in the corresponding hand is decidedly greater than in the normal hand. Secondly, it is very likely that a dilated right subclavian artery offers a freer passage to the blood than the normal left subclavian does. That such reciprocal relations have an important influence on the distribution of the blood is indicated in an interesting manner by the results of the first blood flow examination after ligation of the innominate. On May 22 (eleven days after the operation) the flow in the right hand was 3.44 grams per 100 cc. per minute and that in the left hand 15.38 grams (ratio 1 : 4.47), with room temperature 25.0° C. The flow in the right hand has, of course, been greatly reduced by the ligation, but the interesting point is that the flow in the left hand has been correspondingly increased. Thus, 100 cc. of right hand and 100 cc. of left hand together received 18.88 grams of blood per minute before the ligation and 18.82 grams after ligation, exactly the same amount. But the distribution is totally different. Of course, this extremely exact correspondence is accidental, but it cannot be accidental that the flow in the left hand should have been so much smaller than that in the right before the operation and should have been so greatly increased after it. The cutting off of the path through the innominate and right common carotid obviously permitted more blood to enter the alternative route of the left subclavian and left carotid. That the flow in the left carotid was increased after the operation was indicated by the plainly visible throbbing of the left temporal artery. I have elsewhere discussed[3] the reciprocal effect of occlusion of one path upon the corresponding vascular path on the other side of the body.

The next blood flow examination was made on May 28 (seventeen days after the ligation). The flow in the right hand was 4.76 grams, and in the left 15.31 grams per 100 cc. per minute (for a period of five minutes when the flows were at the maximum for the two hands), with room temperature 26.0° C. The ratio of the

[3] Stewart, *Jour. Exper. Med.*, 1915, xxii, 1.

flows was 1 to 3.21, indicating a steady improvement in the collateral circulation. Including a period of vasoconstriction due to a psychical cause, which of course diminished the circulation more in the left hand than in the right, the flows (for ten minutes) were 4.15 grams per 100 cc. per minute for the right and 12.17 grams for the left hand (ratio 1 to 2.93). The reflex change in the flow elicited in the right hand by immersing the left hand in warm water was small, as is always the case in a part whose circulation is mechanically obstructed. For the three minutes immediately preceding the vasomotor test the flow in the right hand was 4.04 grams per 100 cc. per minute. For the first four minutes of immersion of the left hand in warm water the flow in the right sank to 3.05 grams per 100 cc. per minute, to rise to 4.86 grams per 100 cc. per minute for the remaining four minutes of the period, an insignificant reaction.

On June 4 (twenty-four days after the operation) the flow in the right hand was 4.86 grams and in the left 9.00 grams (ratio 1 to 1.85) per 100 cc. per minute for the last 18 minutes in the calorimeters, with room temperature 23.9° C. The patient came to the hospital for the examination on rather a cool morning, naturally with bare hands, and vasoconstriction due to this was probably responsible for cutting down the flow in the left hand. For the reason already given the effect on the right hand would be comparatively insignificant. The ratio is therefore probably to some extent artificial, and gives an unduly favorable view of the development of the collateral circulation at this time. Nevertheless the fact that in spite of the vasoconstriction the flow in the right hand is absolutely greater than at the last examination shows clearly enough that the collateral circulation is still opening up.

The last examination was made on June 11 (thirty-one days after the operation). The right hand was now being freely used, the only symptoms which troubled the patient being numbness along the palmar surface of the thumb and the radial surface of the index finger. The hand was fairly strong, although not of course as strong as the left hand. The flow in the right hand was 8.55 grams per 100 cc. per minute and in the left 14.24 grams (ratio 1 to 1.66). There was no pulse in the accessible arteries of the right anterior extremity.

The collateral circulation has therefore developed much more rapidly than in the other case. This is doubtless to be attributed in part at least to the youth of the patient and the consequent greater distensibility of his arteries and the greater driving power of his heart.

Protocols.

First Examination of Blood Flow.—Arthur B. May 8, 1915. Hands in bath at 10.27 a. m., in calorimeters at 10.38½, out of calorimeters at 10.51. Pulse 84.

Time.	Temperature of			Time.	Temperature of		
	Calorimeters.		Room.		Calorimeters.		Room.
	Right.	Left.			Right.	Left.	
10.38	31.31	31.21		10.46	31.73	31.39	
10.40	31.36	31.22		10.47	31.79	31.41	22.1
10.41	31.38	31.25	21.4	10.48	31.84	31.425	
10.42	31.42	31.26	21.9	10.49	31.92	31.45	22.5
10.43	31.49	31.28		10.50	31.99	31.47	
10.44	31.56	31.30		10.51	32.05	31.495	22.9
10.45	31.64	31.33		11.02	31.89	31.33	

Cooling of calorimeters in 11 minutes, right 0.16°, left 0.165°. Volume of right hand 482 cc., of left 427 cc. Water equivalent of calorimeters with contents, right 3,480, left 3,436. Rectal temperature 37.65° C.

Second Examination.—May 22, 1915. Hands in bath at 2.11 p. m., in calorimeters at 2.20, out of calorimeters at 2.31. Pulse 100.

Time.	Temperature of			Time.	Temperature of		
	Calorimeters.		Room.		Calorimeters.		Room.
	Right.	Left.			Right.	Left.	
2.19	31.98	31.98		2.27	32.015	32.41	
2.21	31.96	32.02		2.28	32.03	32.48	25.1
2.22	31.97	32.08	25.0	2.29	32.04	32.55	
2.23	31.97	32.14		2.30	32.055	32.62	25.0
2.24	31.975	32.20	25.0	2.31	32.07	32.68	
2.25	31.98	32.26		2.43	31.95	32.54	
2.26	32.00	32.34	25.0				

Cooling of calorimeters in 12 minutes, right 0.12°, left 0.14°. Volume of right hand 485 cc., of left 410 cc. The mark on the left wrist was inadvertently put somewhat lower than usual, so that a somewhat smaller volume of the left hand was in the calorimeter. Water equivalent of calorimeters with contents, right 3,483, left 3,423 cc. Mouth temperature 37.0° C.

Third Examination.—May 28, 1915. Hands in bath at 2.10½ p. m., in calorimeters at 2.22. At 2.36 the left hand was immersed in water at 44° C. At 2.44 the right hand was removed from the calorimeter.

Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.	Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.
2.21	31.95	31.95		2.34	32.09	32.58	25.9
2.23	31.945	31.99	25.9	2.35	32.105	32.63	
2.24	31.96	32.04		2.36	32.12	32.67	
2.25	31.97	32.08	26.0	2.37	32.125		25.7
2.26	31.975	32.12		2.38	32.135		
2.27	31.985	32.16	26.0	2.39	32.14		
2.28	31.99	32.21		2.40	32.15		25.9
2.29	32.005	32.27	26.1	2.41	32.165		
2.30	32.02	32.34		2.42	32.185		
2.31	32.04	32.40	26.1	2.43	32.205		25.9
2.32	32.055	32.47		2.44	32.22		
2.33*	32.08	32.54		2.52	32.14	32.48	

* Here he began to concern himself about the preparations being made for the warm water test, causing some psychical vasoconstriction.

Cooling of calorimeters, right 0.08° in 8 minutes, left 0.19° in 16 minutes. Volume of right hand 458 cc., of left 420 cc. Water equivalent of calorimeters with contents, right 3,461, left 3,431 cc. Rectal temperature 37.44° C.

Fourth Examination.—June 4, 1915. The day was rather cool and the examination was begun soon after his arrival at the hospital. Pulse 78. Hands in bath at 11.33 a. m., in calorimeters at 11.42½, out of calorimeters at 12.05.

Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.	Time.	Temperature of Calorimeters. Right.	Temperature of Calorimeters. Left.	Temperature of Room.
11.42	31.70	31.65		11.56	31.805	31.975	
11.44	31.68	31.66	23.6	11.57	31.82	32.01	
11.45	31.69	31.67	23.8	11.58	31.83	32.04	23.9
11.46	31.695	31.675	23.8	11.59	31.845	32.07	
11.47	31.70	31.70		12.00	31.855	32.09	
11.48	31.71	31.74	24.0	12.01*	31.875	32.14	24.0
11.49	31.73	31.78		12.02	31.895	32.175	
11.50	31.74	31.80	23.9	12.03	31.91	32.19	24.0
11.51	31.75	31.83	24.0	12.04	31.925	32.23	
11.52	31.755	31.85		12.05	31.95	32.275	
11.53	31.76	31.88		12.13	31.84	32.16	
11.54	31.775	31.92	23.9				
11.55	31.795	31.95					

*Here he is beginning to fidget and says the right arm and hand are getting tired.

Cooling of calorimeters in 8 minutes, right 0.11°, left 0.115°. Volume of right hand 446 cc., of left 413 cc. Water equivalent of calorimeters with contents, right 3,452, left 3,425. Rectal temperature 37.19° C.

Fifth Examination.—June 11, 1915. Pulse 84. Hands in bath at 11.03 a. m., in calorimeters at 11.12¾, out of calorimeters at 11.30.

Time.	Temperature of Calorimeters. Right.	Left.	Room.	Time.	Temperature of Calorimeters. Right.	Left.	Room.
11.12	31.77	31.74		11.23	32.10	32.29	
11.14	31.80	31.79	25.0	11.24	32.13	32.35	25.1
11.15	31.84	31.85	25.1	11.25	32.165	32.41	
11.16	31.88	31.91		11.26	32.20	32.46	25.1
11.17	31.905	31.97	25.0	11.27	32.24	32.515	
11.18	31.93	32.02		11.28	32.26	32.56	
11.19	31.965	32.075		11.29	32.29	32.61	
11.20	32.00	32.135	25.0	11.30	32.32	32.66	
11.21	32.04	32.18		11.37	32.235	32.57	
11.22	32.07	32.24					

Cooling of calorimeters in 7 minutes, right 0.085°, left 0.09°. Volume of right hand 457 cc., of left 425 cc. Water equivalent of calorimeters with contents, right 3,460, left 3,435 cc. Rectal temperature 36.91° C.

SUMMARY.

The development of the collateral circulation after ligation of the innominate and right common carotid arteries for subclavian aneurysm was studied in two cases by measuring the rate of blood flow in the hands from time to time.

In a woman, sixty-eight years old, the flow in the right hand three weeks after the operation was two-sevenths of that in the left. Nineteen weeks after the operation the flow in the right hand was more than three-fourths of that in the left, although no pulse returned until long afterwards.

In a man, twenty-five years old, the flow in the right hand eleven days after the operation was between one-fourth and one-fifth of that in the left. Seventeen days after the operation the flow in the right hand was nearly one-third of the flow in the left. Twenty-four days after the operation the flow in the right hand had increased to more than one-half of the left hand flow. Thirty-one days after the operation the flow in the right hand was three-fifths of that in the left, without return, as yet, of any pulsation.

Before the operation the flow in the right hand was markedly greater than in the left, notwithstanding the small size of the right radial pulse as compared with the left. The explanation of this fact is discussed.

Report of a Case of Rheumatic Endocarditis complicated by Multiple Emboli and Thrombosis in which Blood Flow Determinations Were Carried out, with a Report of the Autopsy Findings

By R. W. SCOTT, M. D., and G. N. STEWART, M. D., from the City Hospital and the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland.

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REPORT OF A CASE OF RHEUMATIC ENDOCARDITIS COMPLICATED BY MULTIPLE EMBOLI AND THROMBOSIS, IN WHICH BLOOD FLOW DETERMINATIONS WERE CARRIED OUT, WITH A REPORT OF THE AUTOPSY FINDINGS

By R. W. SCOTT, M. D., and G. N. STEWART, M. D., from the City Hospital and the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland.

The following case was studied first at Lakeside Hospital and later at the City Hospital. It was deemed worthy of publication not on account of its rarity, but because it presented certain interesting clinical features, some of which were difficult to explain during life. These were readily interpreted in the light of the facts obtained from the post mortem examination, together with a series of blood flow determinations made in the hands and feet at intervals during the clinical course of the disease, which observations afforded a means of quantitatively estimating the impairment in the circulation.

Clinical History. The patient, Costa B., male, aged 47, first came under observation April 30, 1914, in the service of Doctor Hoover, to whom we are indebted for the opportunity of studying the case while at Lakeside Hospital.

On admission the man was suffering from an attack of acute rheumatic fever, involving the right knee and ankle. He gave a history at this time of having always been well prior to the onset of his present trouble. There was no demonstrable cardiac enlargement and no abnormal precordial activity palpable. A loud blowing systolic murmur was audible at the apex, otherwise the heart sounds were clear. He was given sodium salicylate to the point of toxicity, following which his temperature returned to normal, the inflammatory process in the joints abated, and he was discharged from the hospital May 9, 1914, feeling perfectly well.

Contrary to advice, he began to work the day following his discharge and worked steadily until July 31, 1914, when he was seized with a sudden attack of pain in the right leg, most severe in the region of the groin. He fell to the floor and was taken to the hospital in an ambulance.

Examination of the heart at this time showed a slight enlargement to the left, but no enlargement upward or to the right was demonstrable. There was a presystolic crescendo murmur running up to and ending in a loud and sharp first sound. A faint blowing systolic murmur followed the first sound. The second sound was clear. Palpation of the accessible arteries revealed an absence of the pulse in the left brachial and radial, with a normal pulse in the corresponding vessels of the opposite side. A good pulsation was present in the right femoral and popliteal, but absent in the dorsalis pedis and only faintly perceptible in the tibialis anticus on the right side. All the other palpable arteries showed a good pulsation. The following notes were made during the patient's stay in the hospital at this time.

August 4, 1914.—Patient is complaining of pain in the left elbow and right groin. Pulsation in the left radial artery is faintly perceptible. Pulsation in the brachial is normal. Pulsation has returned in the right dorsalis pedis.

September 1, 1914.—Patient is feeling well, although there is no pulsation in the left radial or right dorsalis pedis.

September 26, 1914.—Left arm is very painful. Still no radial pulse perceptible.

September 30, 1914.—Right radial pulse is diminished in volume, but brachial pulse normal.

October 3, 1914.—There is no pulsation in the left radial or brachial arteries. Patient is still complaining of pain in the right leg.

October 5, 1914.—The right radial pulse is absent.

October 8, 1914.—Right radial pulse returned to normal volume.

October 10, 1914.—The left radial pulse is absent. Patient is complaining of pain in the left shoulder and down the left arm as far as the elbow.

November 20, 1914.—Patient discharged. The pulse in all the accessible arteries is normal except in the left radial artery, where it is diminished in volume, and the right dorsalis pedis, where it is absent.

The patient was not observed again until February 2, 1915, when he entered the City Hospital in the service of Doctor E. P. Carter*, complaining of pain is the left arm and right leg, the pain being particularly severe with exercise. Since his discharge (Nov. 20, 1914), he had remained fairly comfortable but was unable to work, on account of the pain in the right leg when he attempted to walk. Examination showed a marked atrophy of both the left arm and the right leg, with no pulse in any of the accessible arteries of either extremity. The left hand and right foot were slightly cyanotic, and felt cold to touch. The pulse in the right radial and brachial was diminished in volume. No abnormality in the volume of the pulse was made out elsewhere.

The cardiac findings were the same as above noted on the previous admissions, except for the occurrence of occasional premature beats of auricular origin as shown by polygraphic tracings. Blood culture was negative on two different occasions. Temperature oscillated between 99 and 100.5° F. With the exception of a slowly progressive atrophy of the right leg, very little change was noted in the patient's general condition for three months, at which time (May 1) he developed extreme pain in both lower extremities, with a loss of the patellar and achilles reflexes on both sides. There was so much superficial tenderness that he would not tolerate the pressure of the bed clothes. This was interpreted as being due to an ischaemic condition of the peripheral nerve trunks incident to the extreme impairment in the mass movement of blood through the lower extremities. The right leg became much discolored. He died on May 4.

Clinical Diagnosis. Infectious endocarditis with stenosis and insufficiency of the mitral valve multiple emboli and thrombosis; terminal edema of the lungs and gangrene of the right foot and leg.

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*Footnote—We desire to acknowledge the courtesy extended to us by Doctor Carter in our study of this case.

Autopsy Findings Bearing on the Case. The heart showed extreme dilatation and hypertrophy of the left auricle; the wall in some places measured 3 mm. in thickness. The mitral valve measured 10 cm., and displayed a marked grade of fibrotic thickening of both leaflets, while between the two there was situated a round mass of fresh, soft vegetation measuring 3 cm. in diameter. The mitral orifice measured 1½ cm. across. Minute dissection of the coronary arteries revealed nothing abnormal. In the left subclavian artery just at the origin of the vertebral artery there was an old and completely organized thrombus entirely obliterating the lumen of both the subclavian and vertebral arteries on that side. The right brachial artery for a distance of 8 cm. above the bend of the elbow was hard and thickened, with a lumen just large enough to admit the passage of a small probe. The right common iliac artery through its whole course and the first 8 cm. of the external iliac were completely filled with a partially organized thrombus which totally obstructed the circulation. The right femoral artery appeared as a hard fibrous cord and was about half the size of the left femoral. The left common iliac was not involved, but lodged in the left external iliac at its origin was a fibrinous mass 2 cm. long. completely occluding the lumen, but not adherent to the walls of the artery.

Microscopic Examination. A section from the site of obstruction in th subclavian showed the lumen completely filled with a mass of vascularized connective tissue, which in a few places was young and of the type of early organization tissue with lymphocytes and endothelial cells, but for the most part was of older, denser type, showing small spindle-shaped nuclei and well-developed fibrillar substance. Numerous endothelial cells contained hemosiderin granules. The intima was somewhat thickened; the internal lamina was necrotic. The media and adventitia were fibrotic.

A section of the right brachial showed its lumen almost obliterated with dense fibrous tissue, in the center of which was a distinct slit-like canal. No trace of a thrombus remained. The internal elastic lamina was almost complete, being interrupted at only one place, and only for a short distance. In the periphery of the thickened intima were several smaller blood channels, near which was a deposit of blood pigment. The thrombus from the right common iliac was almost completely hyalinized, showing dense, irregular bands of hyalin, with here and there in meshes masses of basophilic nuclear debris. Irregular bands of new connective tissue extended for a short distance into the thrombus from the wall of the artery. These bands contained delicate capillaries and showed an old central thrombus made up of finely granular acidophilic necrotic material, containing a few granules of hemosiderin. Both sides of the thrombus showed a moderately thick layer of organized tissue, which had gone on to the formation of fairly dense old connective tissue, containing large capillaries and a considerable number of lymphocytes and endothelial cells, many of the latter containing granules of hemosiderin. The intima was markedly thickened and hyalinized.

The media was fibrosed and hyalinized and showed atrophy and disappearance of its muscle. The adventitia also showed hyalinization of its connective tissue.

The first examination of the blood flows in the hands and feet was made on October 26, 1914. The flow was found to be 6.03 gm. for 100 c.c. of part per minute for the right hand and 1.28 gm. for the left hand, with room temperature 22° C. No pulse could be detected at the left wrist. The ratio of the flow in the left hand to that in the right was 1 :4.71. The flow in the left hand is perfectly compatible with complete obstruction of the left subclavian at this time. For, in a case of ligation by Doctor Hamann of the innominate and the common carotid for subclavian aneurysm in a man 25 years of age, the flow in the right hand, 11 days after the operation, was already 3.7 gm. per 100 c.c. of hand per minute (about one-quarter of the flow in the left hand) ; and in a woman 68 years old, on whom Doctor Hamann performed the same operation, the flow in the right hand a month after the operation was over 1.5 gm. (about two-sevenths of the flow in the left hand).

If, as the absence of pulsation in the radial and the small blood flow in the left hand indicate, the left subclavian was totally plugged at the time of the first blood flow examination, the block could hardly have been entirely due to such a complete organized thrombus as was found at autopsy. For, on November 20, 1914, a pulse was detected in the left radial, although it was diminished. At some time between the patient's discharge from Lakeside, on that date, and his admission at City Hospital, the obstruction in the left subclavian, it is to be assumed, became complete and permanent.

The flow in the feet of Costa B. on October 26 was 1.25 gm. for the right and 2.50 gm. for the left (ratio 1 : 2). This ratio was the highest observed in the series of examinations. Later on the ratio altered unfavorably to the right foot. Accordingly, there is every reason to suppose that at this date the obstruction on the arterial path of the right leg was less complete than it afterwards became.

The flow in the right hand is subnormal for the man's age. This would fit in with the existence at this date of a certain degree of obstruction on the arterial path of the right arm, such as was revealed at the autopsy. However, it must be remembered that the man's heart was handicapped, and if we compare the flow in the left foot, where there is no evidence of any ob-

struction, with that in the right hand, the ratio (1 : 2.4) is not abnormally small, as it ought to be if the path to the right hand was obstructed to any material extent at this time.

The second examination, made on February 24, 1915, showed a great improvement in the blood-flow in the left hand, notwithstanding the absence of pulsation in the accessible arteries of the limb. The flow in the left hand was 2.54 gm. and in the right 6.96 gm. per 100 c.c. of part minute (ratio 1 : 2.74), with room temperature 23.8° C. The improvement, both absolute and relative, in the flow in the left hand, is quite compatible with the existence at this time of complete block of the subclavian and with complete absence of pulsation in the part. The opening up of the collateral circulation after ligation of the innominate in the old lady mentioned raised the blood-flow in the right hand in the course of 16 weeks so much that the ratio between the flow in the right and left hands became 1 : 1.3 instead of 1 : 3.5, although it required a far longer time for pulsation to return.

At the third examination of Costa B, on February 26, 1915, the flow in both hands was increased, being 3.7 gm. per 100 c.c. per minute in the left and 9.98 gm. in the right, with room temperature 24° C. The ratio of the flows in the two hands was practically the same as at the second examination, indicating that the increased flow was due to increased output of the heart. The pulse rate was 102 at the third as compared with 81 at the second examination. The flow in the left foot was 6.5 gm., a marked increase, but that in the right foot was only 0.7 gm. per 100 c.c. per minute. The ratio of the flows in the two feet was 1 : 9.28, showing a great deterioration in the circulation of the right foot and no doubt of the whole leg since the time of the first examination.

All the other clinical signs (increased coldness of the foot, increased pain in the leg, etc.) supported the conclusion that the circulation had become worse. There was, however, no gangrene and blood-flows even smaller have often been measured in the absence of gangrene. The interesting fact that the sum of the flows in the two feet bears precisely the same ratio to the sum of the flows in the two hands, as was the case four months previously, suggested that "the blocking of the vascular path to one leg (doubtless the diminution in the flow extends to the whole of the right posterior extremity) is associated with a reciprocal dilatation of the path to the other leg, so that the normal parti-

tion of the blood between the legs and the rest of the body is scarcely disturbed. That is to say, the blood which normally finds its way through the two common iliacs seems eventually, when the main part of the path from one common iliac is blocked, still to find its way through the one which remains pervious, the normal limb making room . . . for an additional quantity of blood."*

It will be seen that the suggestion as to the position of the block was confirmed by the autopsy findings.

The fourth examination was made on April 7. The details have not hitherto been published and are given in the table.

Blood-flow examination of Costa B., April 7, 1915. Pulse 132. He says he fells very warm. Feet in bath at 2:34 P. M., in calorimeters at 2:51, and out of calorimeters at 3:07½ P. M.

	Temp. of Calorim's				Temp. of Calorim's		
Time	Right	Left	Room	Time	Right	Left	Room
2:49	32.59	32.92		3:05	32.50	33.96	23.3
2:53	32.55	33.10	24.1	3:07	32.48	34.10	
2:55	32.525	33.25	23.5	3:10	32.42	34.09	
2:57	32.52	33.41	23.0	3:24½	32.03		
2:59	32.515	33.56	23.1	3:26½		33.72	
3:01	32.51	33.71	23.3				
3:03	32.505	33.82	23.4				

Cooling of calorimeters, right 0.39° C. in 14½ minutes, left 0.37° C. in 15½ minutes. Volume of right foot, 1194 c.c., of left foot, 1225 c.c. Water equivalent of foot calorimeters with contents, right 3858, left 3881.

Hands in bath at 3:30 P. M., in calorimeters at 3:38½, out of calorimeters at 3:47 P. M.

	Temp. of Calorim's				Temp. of Calorim's		
Time	Right	Left	Room	Time	Right	Left	Room
3:37	32.48	32.49		3:44	32.82	32.50	24.5
3:39	32.49	32.48	24.3	3:45	32.87	32.51	24.6
3:40	32.53	32.46		3:46	32.94	32.52	24.7
3:41	32.62	32.48	24.5	3:47	33.05	32.53	
3:42	32.69	32.49	24.6	3:56	32.93	32.41	
3:43	32.76	32.50	24.6				

Cooling of hand calorimeters, right 0.12° C., left 0.12° C. in 9 minutes. Volume of right hand 489 c.c., of left 452 c.c. Water equivalent of hand calorimeters with contents, right 3486, left 3456. Rectal temperature, 38.75° C.

*Footnote—Quotation from a paper by one of us on "A Study of inequalities in the blood-flow in the two hands (or feet) due to mechanical causes (embolism, compression of vessels, etc.) or to functional (vasomotor) causes, with a discussion of the criteria by which the conditions are discriminated," received for publication by *The Journal of Experimental Medicine,* March 17, 1915.

The patient felt very warm. In accordance with this, the blood-flow in the right hand was increased to 13.11 gm., much the largest flow seen in this case. The increase was no doubt due largely to cutaneous vasodilatation, which of course affected the flow in the left hand but little on account of the great resistance introduced by the mechanical block. The flow in the left hand (3.43 gm.) was even slightly less than at the last examination. This amount is perfectly sufficient to nourish a resting hand, and the hand did not trouble him. In the feet the flows were 1.51 gm. and 7.43 gm. for the right and left, respectively (ratio 1 : 4.92). A certain improvement in the collateral circulation of the right foot since last examination is indicated, and the clinical condition of the limb agreed with this. There was no sign of gangrene, the atrophy of the leg previously noted seemed marked, and the volume measurement showed little if any atrophy of the foot. Notwithstanding the fluctuation in the absolute amounts of the blood-flow in the hands and feet, the ratio of the combined foot flows to the combined hand flows remained practically the same (1 : 1.85) as at the previous examinations.

A natural explanation of the alternate deterioration and improvement in the circulation in the right foot revealed by the blood-flow measurements is afforded by the autopsy findings. It would seem probable that the block in the common iliac was complete before or about the time of the third examination (February 26). It is well known that after ligation of the common iliac a collateral circulation for the leg develops through various channels, e. g., the lumbar arteries. Opening up of this collateral circulation might have been responsible for the improvement noted at the last examination on April 7. Possibly some part of the circulation came from branches of the internal and external iliacs of the opposite side. If so, the lodgment of the fresh embolus in the left external iliac a few days before death would explain the impairment of the circulation noted in the left leg, as well as the gangrene of the right leg and foot. Of course, it is not known whether this freely movable embolus, although found at autopsy in the left external iliac, might not have lodged at or above the bifurcation, interfering there with the collateral circulation to the right leg (e. g., through the lower lumbar arteries) and the direct circulation to the left leg. It is assumed that the obstruction in the right common iliac was total before this time. If a small amount of blood was getting past this obstruction, the fresh

embolus, lodging at the bifurcation, would cut off this supply and lead to the acute symptoms which preceded death.

From the point of view of prognosis, the blood-flow measurements in such cases, although they cannot, of course, give warning in advance of fresh obstructions, are capable of answering the question whether, after an obstruction has occurred, the diminution in the circulation is nearing the danger point or whether there is a good margin of safety. Successive measurements will also give information as to whether the circulation is expanding satisfactorily or the reverse. In the case described, for example, the measurements indicated all along that the flow in the anterior extremity was sufficient for nutrition and was improving, whereas in the posterior extremity the first blood-flow observed was most satisfactory, and afterwards there was evident deterioration.

Sometimes the question whether an obstruction has occurred may be in doubt, and then a blood-flow measurement might help to clear the matter up. Thus, in a case of mitral stenosis* in a boy 17 years of age, height 4 feet 10¾ inches, the question arose whether certain symptoms in the left leg and foot might not be due to embolism. The blood-flow examination showed, however, that the circulation in the left foot was rather better than in the right, and the ratio of the flow in the left foot (or of the average of the two feet) to the average flow in the hands was within the normal limits, indicating no such definite deficiency as must have been associated with embolism. The flow in the right hand (for the last 12 minutes in the calorimeter) was 10.56 gm. per 100 c.c. of part per minute, in the left hand 10.21 gm. (average for the two hands 10.38 gm.), with room temperature 26.8° C.

In the right foot the flow (for the last 10 minutes in the calorimeter) was 2.54 gm. per 100 c.c. per minute, and in the left foot 3.12 gm. (average for the two feet 2.83 gm.), with somewhat lower room and calorimeter temperature. The flows, both in hands and feet, are within the normal range, although, if anything, somewhat scanty for the age of the patient and the room temperature. Compensation was fairly established at the time of the examination.

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*Footnote—I am indebted to Doctor Blankenhorn of Lakeside Hospital for calling my attention to this case. G. N. S.

Feet in bath at 2:00 P. M., in calorimeters at 2:16, out of calorimeters at 2:49. 2550 c.c. water in each calorimeter. The day was rather warm.

Time	R	L	Room	Time	R	L	Room
2:15	31.47	31.45		2:35	31.52	31.56	26.1
2:17	31.42	31.455		2:37	31.53	31.60	
2:19	31.43	31.455	26.2	2:39	31.56	31.64	26.2
2:21	31.435	31.455	26.2	2:41	31.59	31.67	26.2
2:23	31.44	31.46	26.2	2:43	31.61	31.72	
2:25	31.45	31.47	26.1	2:45	31.64	31.755	26.3
2:27	31.46	31.48		2:47	31.68	31.79	26.2
2:29	31.475	31.50	26.1	2:49	31.71	31.85	
2:31	31.49	31.52		2:51	31.69	31.76	
2:33	31.50	31.54	26.1	3:06	31.49	31.55	

Cooling of foot calorimeters in 15 minutes R. 0.20°, L. 0.21° C. Pulse 93. Volume of right foot, 792 c.c., of left, 816 c.c. Water equivalent of foot calorimeters with contents, R. 3336, L. 3354.

Hands in bath at 3:04½ P. M., in calorimeters at 3:13½, out of calorimeters at 3:26.

Time	R	L	Room	Time	R	L	Room
3:13	32.10	32.10		3:21	32.38	32.33	26.8
3:14	32.11	32.11	26.8	3:22	32.41	32.36	
3:15	32.14	32.14		3:23	32.43	32.39	
3:16	32.19	32.17	26.8	3:24	32.47	32.425	26.8
3:17	32.23	32.20		3:25	32.50	32.455	
3:18	32.29	32.23		3:26	32.52	32.48	
3:19	32.32	32.255	26.7	3:33	32.46	32.42	
3:20	32.35	32.29					

Cooling of hand calorimeters in 7 minutes, 0.06° C. Volume of right hand, 321 c.c., of left, 306 c.c. He is right-handed. Water equivalent of hand calorimeters with contents, R. 3352, L. 3340. Rectal temperature, 37.47° C.

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79 (1011)

Demonstration in vitro of the specific affinity of thyroid cells for iodin.

By **David Marine.**

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It is a well-known fact that thyroid tissue in vivo has a specific affinity for iodin. This has been demonstrated in several ways. The simplest and most obvious means is afforded by taking advantage of the spontaneous active hyperplasia of dogs. Having shown that the per cent. of iodin in the gland varies inversely with the degree of active hyperplasia, we were able to demonstrate that the ability of the gland to take up iodin varies with the degree of active hyperplasia present; or if expressed from the viewpoint of chemistry, the ability of thyroid tissue in vivo to take up iodin varies inversely with the degree of saturation of the gland with iodin. Such relatively large proportions of a given intake of iodin may be stored by the thyroid (for example, the recovery of 4.5 mgm. I from a 7.2 gram thyroid lobe in a dog weighing 8 kilos from a total of 50 mgm. KI given by mouth in 10 days) in vivo that it seems likely the surviving thyroid cells in vitro would exhibit this same affinity, and if so it could readily be demonstrated by perfusion.

We have perfused a large series of spleens, kidneys and thyroids of dogs, using defibrinated blood containing ⅓ (by volume) of Ringer's solution. Iodin as KI was added to the perfusion fluid in amounts varying from 5 mgm. to 40 mgm. All perfusions were carried out at temperatures varying between 35° and 37° C. All the thyroid lobes used were goitrous, varying histologically from marked active hyperplasias to colloid goitres, and in weight from 11 to 81 grams. The perfusions were continued from 1 to 2 hours,

and the glands washed with Ringer's for 20 minutes. Iodin and histological examinations were made both on the control and the perfused glands. It was found that relatively large amounts of the KI were held in the thyroid which could not be washed out by the Ringer's solution, while with the spleen and kidney none was held. It was also noted that the amount of KI taken up by a thyroid does not depend on the amount (concentration) of KI in the perfusate. Relatively much less was taken up when 40 mgm. were added to a 75 c.c. perfusate than when 10 mgm. were used. The most interesting observation was that the more marked the hyperplasia (*i. e.*, the less iodin in the gland originally), the more iodin was taken up and also the more rapidly it was taken up, just as in the case of in vivo experiments.

Thus grouping the glands according to their anatomical structure, it was found that from 10 mgm. KI the marked hyperplasias increased their iodin contents over 1,000 per cent.; the moderate hyperplasias increased over 200 per cent.; the colloid early hyperplasias increased over 100 per cent.; and the pure colloid glands about 20 per cent. This is shown more in detail in the following tabulation:

Anatomical Condition of Gland.	No. of Cases.	Average Iodin* per Gm. Before Perfusion.	Average Iodin per Gm. After Perfusion.	Average Increase in Iodin per Gm.	Per Cent. Increase in Iodin.
Marked hyperplasia	5	0.07	0.79	0.72	1,000+
Moderate hyperplasia	3	0.23	0.77	0.54	200+
Colloid early hyperplasia	3	0.47	1.14	0.67	100+
Colloid glands	3	1.03	1.23	0.20	19+

Thyroid glands undergo autolysis in a few hours after removal from the body especially if kept around the body temperature. This is recognized on microscopic examination by a desquamation of the alveolar epithelium. It was found that all such glands not only fail to take up iodin from the perfusate, but lose iodin to the perfusate, a finding that we interpret as meaning that the dead cells have lost the power of storing iodin, or that the taking up of iodin by the thyroid is a property of surviving cells. Studies to determine whether the iodin taken up is as active pharmacologically as the naturally iodized thyroglobulin have not been

* Expressed in milligrams per gram of dried gland.

completed. However, since the amount of iodin taken up by a given perfused gland may be independent of its concentration in the perfusate, and since the amount taken up and the rapidity of its storage varies directly with the degree of active hyperplasia, and since only anatomically intact glands exhibit this characteristic, and since kidneys and spleens perfused under similar conditions do not take up iodin, we believe one may conclude that the surviving thyroid cells in vitro exhibit the same specific biological affinity for iodin as is manifested by the thyroid cells in vivo.

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THE ABSORPTION OF POTASSIUM IODID BY PERFUSED THYROID GLANDS AND SOME OF THE FACTORS MODIFYING IT

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The data included in this report have to deal with the question: Have the surviving thyroid cells *in vitro* a specific affinity for iodin? It is based upon the conviction that there is abundant proof that the thyroid cells *in vivo* exhibit this specific affinity for iodin, and that this biological characteristic is utilized for the purpose of elaborating a physiological secretion highly important to the host rather than that it is utilized for the purpose of rendering the iodin of the body inert and harmless. A few of the more general facts upon which this conviction is based may be referred to at this time. Thus, it has been proved that the gland readily acquires iodin from any form and manner in which it has so far been administered. The amount taken up is relatively so great that maximum thyroid effects are produced by exceedingly small quantities. The quantity taken up and the rapidity of storage have been found to depend upon the degree of saturation of the thyreoglobulin existing at the time of its administration. That is, the lower the original iodin content, the more rapidly it is stored from a given intake, or if expressed in anatomical terms, the ability of the gland to store iodin varies directly with the degree of active hyperplasia. No other body tissue exhibits such characteristics. There is a fairly constant per cent of iodin necessary for normal gland structure in mammals, and also a relatively constant maximum per cent for mammalian thyroid tissue. As could be inferred from the relatively constant maximum iodin percentage and the relatively

constant minimum per cent associated with normal gland structure, it is found that iodin invariably involutes the physiological hyperplasias of the gland to their colloid or quiescent state; also that it prevents this compensatory overgrowth both in the intact gland and in the stumps of partially removed glands, which otherwise would undergo hyperplasia. This action is exhibited with amounts of iodin so small that many observers are still unable to associate such quantities with any physiological action. However, we have repeatedly seen amounts as low as $\frac{1}{2}$ mgm. of iodin administered by mouth at weekly intervals wholly prevent thyroid overgrowth in pups, while other pups of the same litter living in the same kennel developed well marked goitres.

Oswald had shown that the lowered iodin content was not associated with any demonstrable reduction in the quantity of thyroid protein (thyreoglobulin) with which the iodin is, for the most part, bound. All late work has confirmed this observation, and in addition established the facts that the only known and highly specific physiologic and pharmacologic action of thyreoglobulin is wholly dependent upon its organically contained iodin, and that artificially iodinized albumins and globulins other than the thyroid globulin do not possess this specific action. With these facts in mind—all of which strongly suggest a specific affinity of the thyroid cells *in vivo* for iodin—it seemed likely that certain of these manifestations could be produced *in vitro*, and if so, could be easily demonstrated. The thyroid seems still more favorable for such a demonstration when one recalls that seemingly more difficult functional characteristics of surviving cells of more complex organs, as for example the synthesis of hippuric acid by the kidney, and the production of glycogen from dextrose and of urea from ammonium carbonate by the liver cells, have been demonstrated experimentally.

The method of perfusion was chosen because of its simplicity and because similar operations can be carried out *in vivo*. In all these experiments the thyroids, kidneys and spleen of dogs were used. Up to the present 33 experiments have been made.

No anatomically normal glands were used, primarily because of the difficulty of obtaining them in this region, secondly because

of the technical difficulty of preparing and perfusing so small a structure, and lastly because colloid glands (goitres) have all the physiological characteristics of normal glands and are readily obtained. For studies in thyroid function one needs only physiologically active hyperplasias and the physiologically normal glands free from degenerative changes, of which hemorrhage and cyst-formation are the most common.

The perfusion apparatus used is represented in the accompanying diagram (fig. 1). It was arranged so that it could be sterilized in an ordinary autoclave after being set up for an experiment. A Luer syringe of 10 cc. capacity, with an especially wide nozzle, was used as a pump. Power was obtained from a motor so geared that the number of pump strokes per minute could be adjusted to any rate between 18 and 60. The length of stroke (volume of fluid pumped) was also adjustable from 0.1 to 5 cc.

A mercury manometer was connected with the arterial system, and also served as an elastic cushion, since as little rubber as possible was used in the various connections. In the preliminary experiments 65 cc. of Ringer's solution plus 10 cc. of erythrocytes was used, while in all of the experiments here reported 50 cc. of defibrinated blood and 25 cc. of Ringer's solution were used. This was for convenience only. The circulatory system from the reservoir to the organ box held 25 cc., and as a practical measure it was found best to use Ringer's in getting out the air and in testing the vessels for clots before the blood was introduced into the reservoir.

Oxygen was introduced into the reservoir at first from above, and allowed to rise through a column of glass beads, through which the venous blood also had to pass in the opposite direction. This method of introducing oxygen was sufficient to supply the oxygen needs of the thyroid, but it was found quite inadequate for organs requiring large amounts of oxygen, like the kidney and spleen. Introducing the oxygen from below and allowing it to bubble through the column of blood in the reservoir relieved this difficulty. Frothing was controlled by a perforated porcelain disc placed in the reservoir well above the level of the blood,

and onto this disc the venous blood from the organ was allowed to fall.

The blood flow was kept constant for all thyroid lobes over 15 grams in weight and for all kidneys and spleens—approximately 8 cc. per minute. Three difficulties common to perfusions may be mentioned. First is the occasional occurrence of

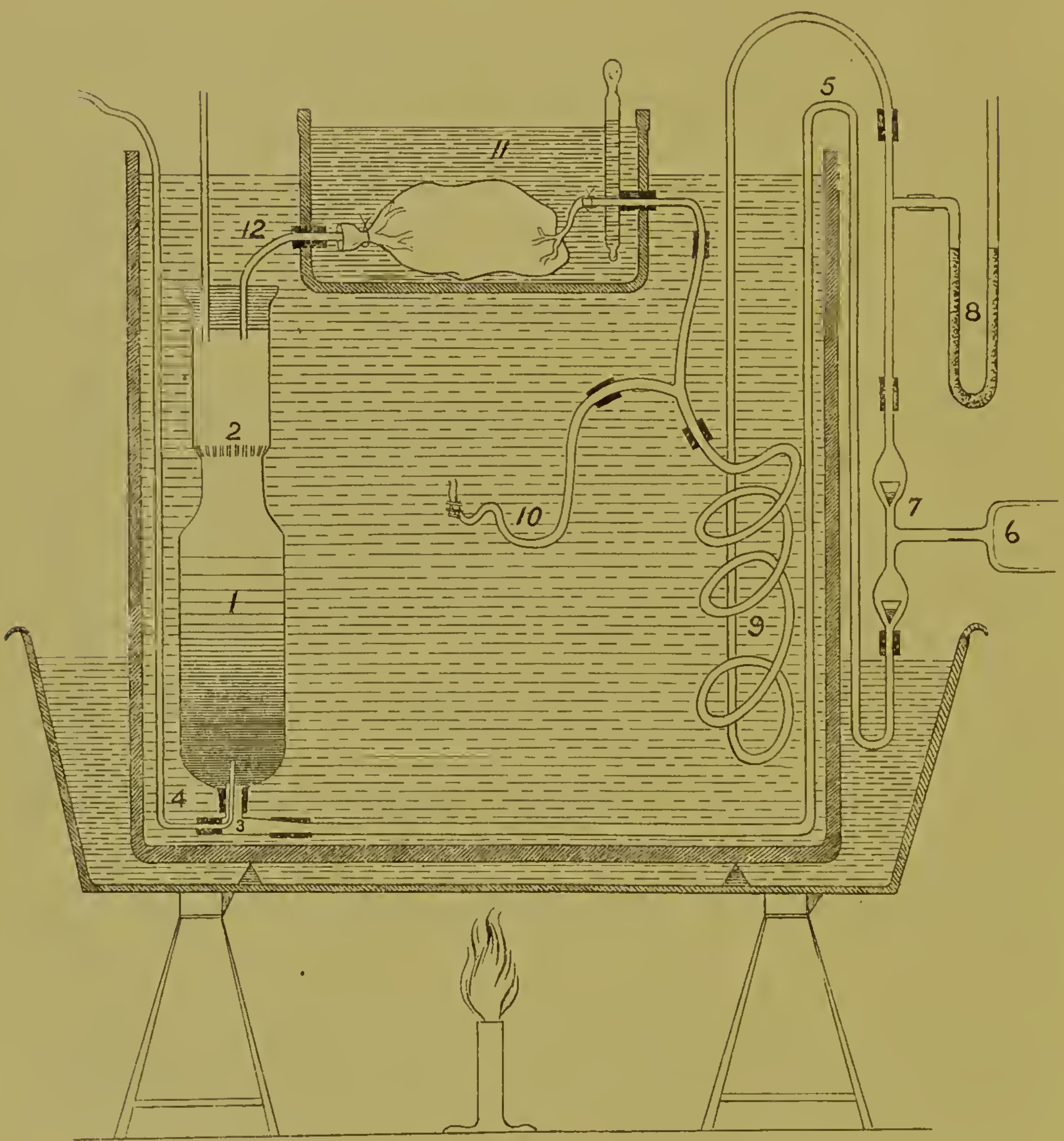

Fig. 1

1, Reservoir; *2*, perforated disc; *3*, outlet for blood; *4*, oxygen tube entering through outlet; *5*, tubing to pump; *6*, pump; *7*, valves; *8*, manometer; *9*, warming coil; *10*, shunt tube; *11*, organ box; *12*, venous backflow to reservoir.

clots in the veins or arteries. The second difficulty is in carefully dissecting and ligating all vessels save the superior thyroid artery and all veins other than those joining the internal jugular from the thyroid. We were surprised, however, to find it easier to obtain thyroid preparations free from leaks and with adequate veins (the thyroid is singular among the organs in the number and great size of its veins) than splenic or renal perfusions. Anomalous arrangements of the thyroid veins occasionally render a lobe unsuitable for perfusion. The same trouble occasionally arises in the case of the spleen and kidney.

Thirdly, oedema in varying degrees is present in all cases. This is most marked with the kidney and spleen and least with the thyroid. Good thyroid preparations perfuse readily at 20 to 50 mm. Hg. pressure after the initial serum constriction of the arteries, which usually passes off in from 6 to 10 minutes. During this period the pressure may rise to 85 or 100 mm. Hg. With the low pressures one may perfuse the thyroid from 2 to 3 hours with less than 10 per cent increase in weight. With the spleen and kidney the necessary pressure is always much higher, although both show the usual transient serum constriction of the vessels. In our experiments the average pressure for the kidney was 80 to 100 mm., while with the spleen it was 70 to 90 mm. The richer and freer lymphatic drainage of the thyroid, together with the short wide capillary system and consequent short circulation time, compensates for the increased permeability of the vessels of surviving organs. Likewise the kidney with its very long and narrow capillary system and the spleen with its relatively long, pecular and ill understood capillary system, together with the fact that all lymphatics are necessarily ligated, offer little or no compensation against the endothelial injury. Upon the whole, the goitrous thyroid probably gives the easiest and most satisfactory perfusion of all the body glands.

In young dogs with actively hyperplastic glands, it is usual to obtain perfusions free from signs of leaks even after two hours. With colloid glands or glands with thickened capsules, slight capillary extravasations of blood into the surrounding Ringer's solution are frequently seen. With the kidney and spleen, even

though using greater care than with the thyroid, we have never been able to prepare them so that no escape of blood took place during the perfusions. Doubtless the difference in pressure necessary for thyroid perfusions, on the one hand, and for kidney and spleen, on the other, account in part for this difficulty.

Histological examinations were made both of the perfused and of the control organs, and the groups have been made as in previous work on the basis of the histological condition. For convenience, four arbitrary thyroid groups have been made, viz.: (1) marked hyperplasia; (2) moderate hyperplasia; (3) early hyperplasia; and (4) colloid glands. The iodin determinations have been brought into relationship with these groups.

Histological examinations have proved a reliable additional check on the physiological condition of the gland cells. Hyperplastic glands often undergo autolysis within an hour or two after removal from the body. This is characterized by desquamation of the follicular epithelium, and, as will be seen later, is associated with a loss of thyroid iodin rather than a gain in iodin during perfusion.

The thyroids, spleens and kidneys were carefully dissected and placed in Ringer's solution in the ice box. Perfusions were usually conducted for about one hour—the shortest being 38 minutes and the longest 5 hours and 30 minutes. Potassium iodid was the only form of iodin used. This salt was used in amounts varying from 5 to 32 mgm. in a total perfusate of 75 cc. Following the perfusion the gland was washed with warmed Ringer's until the fluid came away clear. This usually required from 500 to 1000 cc., depending somewhat on the size of the gland and its histological condition. The same technique was carried out with the kidney and spleen perfusions.

The following protocol is introduced to illustrate the method and data obtained.

Experiment 11, November 5, 1914. Bull-terrier; female; weight, 14.6 kg.

9.50. Etherized, bled, defibrinated.

10.30. Right lobe of thyroid removed; weight 16.5 grams. In Ringer's in ice box.

10.45. Spleen removed; weight, 116.0 grams. In Ringer's in ice box.

11.00. Left kidney removed; weight, 66.0 grams. In Ringer's in ice box.

Left thyroid removed; weight, 16.0 grams. In Ringer's in ice box.

11.20. Perfusion of right thyroid started. 50 cc. defibrinated blood + 25 cc. Ringer's + 5 mgm. KI.

11.23. Pulse, 22; drops per minute, 134; pressure, 72.5; temperature, 35.

11.30. Pulse, 22; drops per minute, 134; pressure, 55; temperature, 36.

12.00. Pulse, 22; drops per minute, 135; pressure, 50; temperature, 37.

12.20. Perfusion stopped. Weight of lobe = 20 grams. Washed with 570 cc. Ringer's. Spec. for iodin and histology; gland, organ box fluid and total fluids.

Left thyroid not perfused.

2.10. Perfusion of left kidney using 25 cc. Ringer's + 50 cc. defibrinated blood + 5 mgm. KI.

2.15. Pressure = 92 mm.; pulse, 22; drops, 106.

2.25. Pressure = 85 mm.; pulse, 22; drops, 110; temperature 36.

3.00. Pressure = 85 mm.; pulse, 22; drops, 110.

3.10. Perfusion stopped. Weight of kidney 98 gm. Washed with Ringer's. Spec. for iodin and histology; gland, organ box fluid and total fluids.

4.05. Perfusion of spleen using 25 cc. Ringer's + 50 cc. defibrinated blood + 5 mgm. KI.

4.07. Pulse, 22; drops, 78; pressure, 90; temperature, 34.5.

4.20. Pulse, 22; drops, 89; pressure, 76.

5.05. Perfusion stopped. Weight of spleen, 162 grams. Washed and spec. for iodin and histology.

Histology. Thyroid, colloid—early hyperplasia. Structure well preserved. Kidney, oedematous. Spleen, highly oedematous.

Iodin.	Right thyroid (perfused)	= 1.38 mgm. per gram. dried.
	Left thyroid (not perfused)	= 0.54 mgm. per gram dried.
	Kidney (not perfused)	= 0.00 mgm. per gram dried.
	Spleen (perfused)	= 0.03 mgm. per gram dried.

This is the average protocol and shows the great difference between the thyroid, on one hand, and the spleen and kidney,

on the other, as regards the amount of KI absorbed when exposed to the same amounts for the same interval of time. These data for all the experiments of this type are collected in the following table.

TABLE I

HISTOLOGICAL CONDITION	NO. OF PERFUSIONS	IODIN CONTENT PER GM. IN MGM. CONTROL LOBE			IODIN CONTENT PER GM. IN MGM. PERFUSED LOBE			AVERAGE INCREASE PER GM. IN MGM.	PERCENTAGE INCREASE
		E.	M.	Av.	E.	M.	Av.		
(a) Thyroid perfusions									
Marked hyperplasias..........	6	0.00 0.09	0.08	0.07	0.22 1.31	0.85	0.59	0.52	743
Moderate hyperplasias..........	4	0.01 0.38	0.10	0.15	0.11 1.46	0.54	0.66	0.51	340
Colloid—early hyperplasias.......	3	0.33 0.55	0.54	0.47 1.38	0.73	1.11	1.14	0.67	143
Colloid glands.....	3	0.77 1.54	0.78	1.03	0.86 1.85	0.94	1.22	0.19	18
(b) Kidney perfusions									
	17	0.00			0.00 0.09	0.01	0.03	0.03	
(c) Spleen perfusions									
	8	0.00			0.00 0.08	0.03	0.03	0.03	

In the above table the thyroid experiments have been grouped according to their histological structure, and for comparison the results of the kidney and spleen perfusions have been added.

It will be noted that the thyroid takes up KI very rapidly, while the spleen and kidney do so, if at all, only to a slight

degree. We are inclined to think the presence of iodin in any specimen of kidney or spleen indicates either incomplete washing or death of the cells. The iodin taken up by the thyroid cannot be washed out by prolonged washing provided the gland is surviving. The average amount of KI taken up is nearly the same in the three degrees of active hyperplasia, while the percentage increase obviously varies with the degree of hyperplasia. The colloid glands or those nearly saturated with iodin take up very little. No completely saturated glands were used. There is a suggestion that the ability of the gland to absorb KI varies with the degree of hyperplasia and inversely with the iodin content. The differences are too slight to indicate any biological significance or even that the whole process may not be physical. On careful analysis, however, these experiments suggest that other factors are intimately concerned, and it has seemed best to present this analysis under the following groups:

1. Relation of other organs to the absorption of KI.
2. Relation of dying and surviving thyroid cells to the absorption of KI.
3. Effect of varying the concentration of KI.
4. Effect of KCN on the power of the thyroid cells to take up KI.
5. Attempt to wash out the iodin in glands in which the iodin content has been raised by the administration of iodin for a period of two weeks.
6. Effect of *in vivo* perfusions.
7. Is the iodin of either the *in vivo* or *in vitro* perfusions pharmacologically active?

1. *Effect of perfusion of other organs.* Only the kidney and spleen have been used. Normally in these organs one never finds a trace of iodin. As shown in Table I above, the kidney and spleen after perfusion contain only traces, the extremes for the kidney being 0.00 and 0.09 mgm., with a mean of 0.01 mgm. and an average of 0.03. The spleen perfusions were similar. As nearly one half showed no detectable iodin after washing, and in three instances unwashed spleens and kidneys showed a minimum of 0.03 mgm. and a maxmum of 0.08, we are inclined

to consider the small amounts retained as extracellular—either in the vessels, lymphatics or renal tubules. Certainly one can state that the kidney and spleen effects are in no way similar to those of the thyroid.

2. *Relation of dying and surviving thyroid cells to the absorption of KI.* As indices of dying and surviving cells we have used the oxygen consumption and the histological condition of the glands. Both give valuable information, and, so far as our observations have gone, only those glands which were histologically intact maintain their oxygen consuming capacity. All the oxygen determinations were made with the old Barcroft method (5) and were comparisons of the arterial and venous bloods. The thyroid consumes very little oxygen per gram as compared with the spleen, and the kidney has a very high oxygen consumption, as noted by Barcroft.

It was found that the actively hyperplastic glands consumed more oxygen than the colloid glands. This was anticipated and is additional physiological proof that the hyperplastic gland is physiologically more active than the colloid gland. The fact, therefore, that the enormous blood supply of the thyroid has little to do with the oxygen needs of the gland is a matter of the greatest interest and is a point worthy of studying, since the thyroid has so many features in common with the lung—embryological, anatomical and physiological.

The most prominent histological feature of thyroid death is the desquamation of the alveolar epithelium. This histological change is given great prominence in most studies in pathological anatomy, and many speculations as to its significance (e. g., trauma, toxicity, hyperactivity, etc.) have been offered. Our experience leads us to reject all explanations other than that it is an index of cell death and autolysis. Under favorable conditions of asphyxia and temperature, epithelial desquamation may set in an hour after removal from the living dog.

The relation of KI absorption to cell death is shown in the following table.

In those cases with marked autolysis there was always a loss of iodin, although in all cases at least 5 mgm. and in one case

TABLE II

(*a*) *Thyroid perfusions with marked autolysis*

HISTOLOGICAL CONDITION	NO. OF PERFUSIONS	IODIN CONTENT PER GM. IN MGM. CONTROL LOBE			IODIN CONTENT PER GM. IN MGM. PERFUSED LOBE			AVERAGE DECREASE OR INCREASE PER GM. IN MGM.	PERCENTAGE DECREASE OR INCREASE
		E.	M.	Av.	E.	M.	Av.		
Marked hyperplasias..........	2	0.00 0.20		0.10	0.00 ·0.14		0.07	−0.03	−30
Colloid—early hyperplasia........	1			0.38			0.25	−0.13	−34
Colloid glands......	1			0.98			0.54	0.44	−45

(*b*) *Thyroid perfusions with slight autolysis*

HISTOLOGICAL CONDITION	NO. OF PERFUSIONS	E.	M.	Av.	E.	M.	Av.	AVERAGE DECREASE OR INCREASE PER GM. IN MGM.	PERCENTAGE DECREASE OR INCREASE
Marked hyperplasia...........	1			0.08			0.22	+0.14	+175
Colloid—early hyplasia...........	1			0.25			0.40	+0.15	+60

20 mgm. KI were added to the perfusate. In the two cases with mild epithelial desquamation, there was a slight gain recorded, but only about one-fourth that observed in the corresponding grades of hyperplasia with intact glands. It seems certain from these observations that the dying thyroid cells no longer exhibit the power of taking up and holding KI, or, in other words, our experiments indicate that the phenomena of absorption and retention of KI are characteristics of the living cells as judged by the O_2 consumption and the histological structure.

3. *Effect of varying the concentration of KI in the perfusate.* The data are given in the following table arranged according to anatomical structure and KI concentration.

From these figures it would appear that the absorption of KI is independent of the concentration. The lowest amount used was 5 mgm. and the highest 32 mgm. in a constant quantity of

TABLE III

EXP. NO.	IODIN CONTENT PER GM. IN MGM. CONTROL LOBE	IODIN CONTENT PER GM. IN MGM. PERFUSED LOBE	AMOUNT KI USED IN MGM.	INCREASE IN IODIN	PERCENTAGE INCREASE IN IODIN
(a) Marked hyperplasia					
10	0.08	0.97	5.0	0.89	1100+
29	0.09	0.62	10.0	0.53	580+
22	0.08	0.22	10.0	0.14	175+
8	0.08	0.85	12.0	0.77	960+
5	0.00	1.31	17.0	1.31	
33	0.08	0.54	20.0	0.46	575+
(b) Moderate hyperplasia					
27	0.05	0.46	10.0	0.41	820+
7	0.38	1.46	15.0	1.08	280+
13	0.15	0.62	20.0	0.47	310+
4	0.01	0.11	32.0	0.10	1000+
(c) Colloid-early hyperplasia					
11	0.54	1.38	5.0	0.84	160−
12	0.33	0.93	10.0	0.60	180+
9	0.55	1.11	11.0	0.56	100+
(d) Colloid glands					
24	0.77	0.94	10.0	0.17	20+
26	1.54	1.85	10.0	0.31	20−
30	0.78	0.86	10.0	0.08	10+

perfusing fluid—75 cc. There was no histological evidence of autolysis in any of these experiments, and all glands were actively consuming oxygen. No explanation is offered for the wide differences in the amount of KI absorbed, which we believe are greater than could be accounted for on the basis of anatomical differences in the glands or of age and sex.

4. *Effect of KCN on the amount of KI absorbed.* Only two experiments have been made because of the necessity of having dogs with large accessory thyroids which could be utilized as controls for the lobe perfusions. A tabulation of these two experiments follows:

TABLE IV

THYROID LOBE	HISTOLOGICAL CONDITION	AMOUNT KI ADDED IN MGM.	AMOUNT KCN ADDED IN MGM.	IODIN CONTENT PER GM. IN MGM.	DURATION OF PERFUSION	PER CENT GAIN
Exp. No. 32						
Accessory lobe....	Marked hyperplasia...			0.09		
Right lobe........	Marked hyperplasia...	10.0	100.00	0.11	1 hr. 3 min.	20
Left lobe.........	Marked hyperplasia...	10.0	0.00	0.42	1 hr. 3 min.	360+
Exp. No. 33						
Accessory thyroid.	Marked hyperplasia...			0.08		
Right lobe........	Marked hyperplasia...	20.0	50.0	0.08	1 hr.	0.0
Left lobe..........	Marked hyperplasia...	20.0	0.0	0.54	1 hr.	575.0

In these experiments the effect of KCN in inhibiting the absorption of KI is striking. In each case the iodin content of the control and of the lobe treated with KCN are practically the same, while the lobes not treated with KCN gained 360 and 575 per cent respectively. In one experiment 10 mgm. KI was used in the perfusate of each lobe, while in the other 20 mgm. was used. The amounts of KCN used, 100 and 50 mgm., are doubtless far in excess of that necessary to induce the effect, and the result may therefore be merely that of dead cells. They are suggestive that KCN is able to inhibit the cell activity concerned in taking up KI, and it may be another example of the well known action of KCN in inhibiting cell activities in general. Up to the present no opportunity has offered of trying to wash out the KCN and to ascertain whether such glands are again capable of taking up KI—a fact well known in the case of developing eggs (1).

5. *Attempts to wash out the iodin of glands whose iodin contents had been raised by its oral administration for two weeks.*

It is known that iodin is excreted slowly from the thyroid normally, and under certain conditions (developing goitre) may disappear more rapidly. It therefore seemed plausible to at-

tempt to wash out some of it by perfusion, and that by using glands with high iodin contents one would be more likely to recognize its presence in the perfusate, as well as a decrease of iodin in the glands.

It is necessary to separate sharply those glands where the structure was preserved and those which after perfusion showed autolysis and desquamation of the alveolar epithelium, since, as stated above, all glands which showed well marked autolysis showed a loss of iodin whether perfused with or without the addition of KI.

The experiments in which at least one lobe showed preservation of histological structure are given in the following tabulation:

TABLE V

"Wash out" experiments

EXP. NO.	LOBE	WEIGHT IN GMS.	IODIN CONTENT, CONTROL LOBE, IN MGM. PER GM.	IODIN CONTENT, PERFUSED LOBE, IN MGM. PER GM.	TOTAL IODIN IN LOBE	DURATION OF PERFUSION	HISTOLOGICAL CONDITION	TOTAL IODIN IN MGM.
21	Right......	36.5		1.09	10.46	1 hr. 25 min.	Perfect preservation	0.30
	Left.......	28.0		0.85	5.32	1 hr. 15 min.	Moderate autolysis	5.12
23	Accessory.		0.76					
	Right......	22.8		0.98	7.54	1 hr. 38 min.	Perfect preservation	0.52
	Left.......	25.2		0.54	2.99	1 hr. 38 min.	Marked autolysis	4.32
25	Right	19.5		1.54	7.70	1 hr. 2 min.	Perfect preservation	0.25
	Left.......	28.5		1.52	11.37	1 hr. 2 min.	Perfect preservation	0.71
28	Right......	81.0	0.62		13.06			
	Left.......	84.0		0.69	15.87	1 hr. 22 min.	Perfect preservation	Trace

In all cases there was a loss of iodin—lowest in those whose histological structure was well preserved and highest in those showing the most marked autolysis. While such experiments are not conclusive, they suggest that even in surviving glands it is possible to wash out a small percentage of the total iodin, and that as death of the cells takes place, the loss is greatly increased. Under these experimental conditions the loss is entirely through the blood stream. If these experiments are in any sense comparable to what happens in life, it would indicate that the iodin is given off to the blood rather than to the lymph stream. Normally the excretion of iodin in one form and the taking up of iodin in another probably go on simultaneously, and both are under some physiological control. There are many reasons for supposing that this control is exercised through the blood stream directly (2).

6. *Are the results of in vitro perfusions similar to in vivo perfusions?* It is well known, and we have also many times mentioned the fact, that iodin is taken up by the thyroid *in vivo* with great rapidity from any form or mode of its administration thus far tested, but up to the present no attempt at what might be called an *in vivo* perfusion has been made.

The experiments were carried out as follows: One thyroid lobe was removed as a control. Both kidneys were ligated and 50 mgm. KI injected into a vein. After the proper interval of time the dogs were sacrificed and the remaining lobe dissected out and washed with Ringer's. Up to the present but two *in vivo* perfusions of one hour's duration (to compare with the *in vitro* perfusions) have been made.

They may be tabulated as in Table VI.

These results are approximately the same as regards the amount of KI taken up in 1 hour as those obtained with the *in vitro* experiments. The spleens and livers were not washed, and are therefore higher in iodin than the *in vitro* perfusions. These results bear out the many published reports of the distribution of iodin in animal tissues made 24, 48, 72, etc., hours after injection, viz.: that even in one hour the thyroid exhibits its striking selective activity for iodin. One may conclude, there-

TABLE VI

HISTOLOGICAL CONDITION OF LOBES	IODIN CONTENT CONTROL LOBE IN MGM. PER GM.	IODIN CONTENT PERFUSED LOBE IN MGM. PER GM.	IODIN CONTENT SPLEEN IN MGM.	IODIN CONTENT LIVER IN MGM.	TOTAL KI INTRODUCED INTO VEIN	DURATION OF PERFUSION	TOTAL INCREASE IN IODINE IN MGM. PER GM.	PERCENTAGE INCREASE
Moderate hyperplasia..	0.32	0.77	0.06	0.03	50.0	1 hr.	0.45	140
Marked hyperplasia..	0.12	0.48	0.06	0.03	50.0	1 hr.	0.36	300

fore that there is no difference between *in vivo* and *in vitro* perfusions of one hour's duration as regards the thyroid's affinity for KI, and these results by deduction add further evidence of the survival of the thyroid in the *in vitro* perfusions.

7. *Is the iodin deposited in the thyroid either by in vivo or by in vitro perfusions of one hour's duration pharmacologically active?*

This seemed to us a most important question. It is universally accepted that the activity of the thyroid depends on its iodin content, and we have many times demonstrated this by obtaining from the same animal several specimens of thyroid during a course of feeding iodin and found that, as the iodin content rose, the gland showed a corresponding rise in its pharmacological activity. So far as we have been able to ascertain, no tests of the pharmacological activity have been made with thyroid which has been exposed to iodin for less than four days, and in that time the iodin or at least a part of it has become active. In this report we will record our tests for the pharmacological activity of thyroid perfused for one hour both *in vivo* and *in vitro*, using the very sensitive test of Gudernatsch (3), viz., the effect on tadpoles.

The experiments were carried out as follows: Groups of 5 tadpoles were placed in agate-ware dishes and fed with 50 mgm. of the powdered thyroid every other day and fresh sheep liver was given for two-hour periods on alternate days. The perfused and control lobes of seven experiments, including the two *in vivo* per perfusions, were used. The experiments were begun

on May 18, 1915, and terminated on June 29. The water (tap water) was changed twice daily.

To our surprise no difference was noticed between the control and the perfused thyroids of the same animal whether *in vivo* or *in vitro* experiments. There were the usual differences in activity among the several experiments depending on their original iodin content as first noted by Lenhart (4). The iodin acquired by perfusion in one hour, whether *in vivo* or *in vitro*, is wholly inactive and the results are comparable to Lenhart's results with KI alone or KI added to thyroid or to artificially iodized proteins. It is the specific combination of iodin in the thyreoglobulin (probably in the aromatic nucleus of an amino acid) which gives thyroid its specific pharmacological activity.

But as stated above, thyroids which have been exposed to KI *in vivo* for three to four days show a marked increase in activity proportional to the iodin increase. Clearly, then, we have evidence that the elaboration of this iodothyreoglobulin requires a considerable interval of time, and also that its elaboration is probably a highly complex and specific chemical activity of the thyroid.

We do not know as yet whether the thyroid alone is capable of carrying out the complete reaction when given a salt of iodin, as KI, but it would seem that further work might not only answer this question, but indicate as well the length of time required for its elaboration as shown by definite increase in its specific activity on tadpoles.

In some work Dr. Graham has carried out in this Laboratory he noticed in a large series of human thyroids certain specimens whose pharmacological activity in tadpoles was less than it ought to have been on the basis of the iodin contents. At the time we had no explanation to offer, but in the light of the results with the perfused thyroids it seems probable that these human thyroid preparations contained iodin in excess of that specifically bound to the thyroid protein.

SUMMARY

Goitrous thyroids of dogs are perhaps the most easily perfused of all organs under conditions at all physiological. The method of perfusion was primarily utilized to ascertain whether salts of iodin were held in the surviving gland in quantities far greater than in other surviving tissues similarly treated, and if this was true, whether one could not partially involute actively hyperplastic glands *in vitro* as we know invariably happens *in vivo*—the changes in the living animal's thyroid being recognizable in from 36 to 48 hours. We have demonstrated the former, but the latter involves the grave difficulties of maintaining nutrition and of getting rid of products of metabolism. The technical and aseptic problems are readily overcome. We have little doubt that eventually it will be possible to partially involute an actively hyperplastic gland by some such method.

The question of the absorption of other salts than iodin as for example bromides, arsenic, etc., has not been investigated. It is well known that following the administration of bromides the thyroid retains a part temporarily, but it produces none of the effects or activities of iodin.

These experiments have also given an indication that the elaboration of iodothyreoglobulin is a slow and probably complex process, and it is hoped that further study will lead to a definite conception of the minimum interval of time required for its production. Such knowledge for the iodin protein combination might be applicable to other protein compounds with inorganic substances whose chemical nature and function are little understood.

It was early recognized that the thyroid alone might not be able to transform KI into iodothyreoglobulin. This also is a subject for investigation.

The fact that it is possible to wash out very small amounts of the stored iodothyreoglobulin from surviving glands and very large amounts from dying glands is of interest in connection with the old controversy whether the thyroid secretion passes out through the lymphatics or blood vessels. With the technique we have used it was possible to separate the products of lym-

phatic drainage from those of the blood, because the thyroid was placed in a glass box filled with Ringer's solution and without any connection with the blood except for the accidental leaks. Several of these perfusions have gone for two hours with out the escape of any blood into the organ box, although many torn lymphatic trunks opened directly into the box. In the washout experiments no iodin was detected in the "organ box fluid" in those glands free from leaks and surviving. This evidence favors the view that the iodothyreoglobulin is given up directly to the blood stream.

CONCLUSIONS

1. Artificially perfused thyroids take up and retain KI to the same extent that *in vivo* perfused thyroids do.
2. This characteristic is not shared by the liver, kidney, spleen or muscle.
3. The amount of KI retained is independent of its concentration in the perfusion fluid.
4. Only surviving glands exhibit the ability of taking up KI.
5. KCN inhibits this activity of the thyroid.
6. It is possible to wash out with defibrinated blood a very small amount of the iodothyreoglobulin in an hour's perfusion even in intact glands rich in iodothyreoglobulin.
7. Autolyzing glands do not take up KI, and rapidly give up their stored iodin to the perfusate.
8. The KI stored in a thyroid gland form one hour's perfusion, whether *in vivo* or *in vitro,* is pharmacologically inactive.

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QUANTITATIVE STUDIES ON THE IN VIVO ABSORPTION OF IODINE BY DOGS' THYROID GLANDS.

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It is common knowledge that iodine is taken up by the thyroid very rapidly when administered in any form and by any method. It is also known that the amounts taken up from a given intake vary with the size of the gland and the existing degree of hyperplasia. These are statements of fact to the best of our knowledge, but they are also vague generalizations and on that account neither satisfying nor convincing. It is for these reasons that criticisms and doubts have been expressed, and it is for the purpose of supplying definite figures that the following experiments, though somewhat old, are reported.

The plan of the experiments was as follows: With the usual aseptic precautions one lobe was removed, cleaned, and weighed. A weighed portion was kept for histological examination, and the remainder dried at 70° for the determination of its iodine content. 50 mg. of either potassium iodide or sodium iodide were given in 5 mg. doses by mouth for the following ten days; then, after an interval varying from five to eight days, the remaining lobe was removed, cleaned, drained of blood, and weighed. A weighed portion was kept for histological examination and the remainder dried for iodine determination.

Six experiments have the above mentioned constant features, and the principal data are tabulated on the following page.

As regards weight of the animals and size of the thyroid lobes, there is fairly wide range between minimum and maximum. So also as regards sex and age the data are sufficient to indicate that no important change is related to these factors.

The histological condition of the control lobes includes examples of our three arbitrary divisions of the several degrees of hyper-

plasia. It will be noted that with the exception of one (A-285), the second lobe was completely involuted to its colloid or resting stage. This exception happens to be the fifteen day or shortest interval between the administration of iodine and the removal of the lobe, as well as the largest thyroid. As the iodine content per gram is much above that at which hyperplasia disappears, it indicates that the interval of time allowed was a little short of

TABLE.

Experiment No.	Age and sex of dog.	Weight of dog.	Thyroid control lobe or iodized lobe.	Time interval between removal of control and iodized lobes.	Weight of lobe.	Histological condition.	Iodine per gm. of dried gland.	Total amount of KI or NaI administered. (10 days.)	Total iodine in lobe.	Ratio of thyroid weight to body weight.	Total iodine found in iodized lobe.
		kg.		*days*	*gm.*		*mg.*	*mg.*	*mg.*		*per cent*
A289	5 mos. ♀	5.0	Control	16	5.1	Marked hyperplasia	0.08	50.0 KI	0.10	1:980	16.0
			Iodized		6.1	Colloid	4.00		6.10		
A274	Young adult ♀	9.0	Control	18	2.5	Moderate hyperplasia	0.15	50.0 NaI	0.10	1:4500	5.6
			Iodized		2.0	Colloid	5.57		2.48		
A285	Young adult ♀	7.75	Control	15	9.5	Moderate hyperplasia	0.32	50.0 NaI	0.76	1:687	18.5
			Iodized		11.28	Colloid early	2.85		8.54		
A286	Middle aged ♂	8.7	Control	16	8.0	Moderate hyperplasia	0.14	50.0 KI	0.18	1:1641	10.2
			Iodized		5.3	Colloid	3.07		4.05		
A287	Middle aged ♀	10.0	Control	18	2.5	Early hyperplasia	0.52	50.0 KI	0.27	1:5000	7.0
			Iodized		2.0	Colloid	4.90		2.91		
A288	Middle aged ♂	14.6	Control	18	3.0	Early hyperplasia	0.53	50.0 NaI	0.35	1:3842	7.7
			Iodized		3.8	Colloid	3.85		2.61		

that necessary to complete the change. The usual variations in the iodine content of the control lobes in relation to the degree of hyperplasia are present.

The variations in the size of the lobes are more marked than usual and show no constancy. In three the iodized lobes are larger and in the others the control lobes are larger. These variations illustrate one point often emphasized before, that, while iodine generally causes a reduction in the size of the thyroid of

dogs, this is not necessarily the case—the necessary change is the involution.

In figuring the ratio of thyroid weight to body weight, obviously the iodized lobe is used, while the body weights are those taken after the first operation. The iodine contents per gram of dried gland, both for the controls and the iodized lobes, are given in one column. There is considerable variation in the amount of iodine stored per gram of thyroid, with a bare suggestion that the smaller the gland, the higher its iodine content. As to the biological significance of these variations, I have no suggestion. It is probably not a physical phenomenon.

The gain in iodine is in all cases very pronounced, and the figures obtained support the generalization that the thyroid has an extraordinary affinity for iodine up to the point of saturation, which is on the average between 5 and 6 mg. per gram of dried gland for dog thyroids. Passing to the total amounts of iodine recovered, it is obvious that the amount varies with the size of the gland. This also has long been known, and merely indicates that with the amount of iodine and the time of its administration definite, and with other organs, especially the kidney, competing, the surface area for absorption is the largest factor. This feature is brought out more clearly in the ratios of thyroid weight to body weight and in the percentages of the total intake of iodine recovered from the thyroid. In figuring these percentages, 50 mg. KI were figured as 38 mg. iodine, and 50 mg. NaI as 42 mg. iodine.

Another factor than the size of the gland is concerned. Unfortunately the series is too small to show it clearly, but it can be seen by comparing Experiment 289 with 285 and 286, that the more marked the hyperplasia or the lower the original iodine content, the greater the quantity stored. The percentage stored from a definite intake would therefore vary with the size of the gland and its degree of hyperplasia.

It should be added that the liver and spleen in each of these experiments were examined for iodine, but with uniformly negative results. This was to be expected, since the minimum interval between the last dose of iodine and the removal of the organs was five days.

It is recognized that the oral administration of such small

quantities of iodine, even when given in very dilute solution, is more likely to cause losses than when introduced parenterally. With dogs, however, only care is necessary to prevent losses, and absorption of the soluble salts of iodine from the alimentary tract is probably complete.

CONCLUSIONS.

These experiments emphasize the extraordinary affinity of the thyroid tissue for iodine. When one considers that as high as 18.5 per cent of a given intake of iodine by mouth may be recovered from a thyroid whose ratio to the body weight is as 1: 687, it stands alone at present among the specific affinities of tissues for inorganic substances. The results further emphasize the fact that maximum thyroid effects are induced by minimum amounts of iodine. The amount of a given intake absorbed depends, for the most part, on the size of gland and the existing degree of hyperplasia or the degree of saturation with iodine at the time of its administration.

OBSERVATIONS ON THE ETIOLOGY OF GOITRE IN BROOK TROUT.

IV. The Effect of Feeding with Fresh and Stale Liver.

By DAVID MARINE, M.D.

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OBSERVATIONS ON THE ETIOLOGY OF GOITRE IN BROOK TROUT.

IV. THE EFFECT OF FEEDING WITH FRESH AND STALE LIVER.*

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(*From the H. K. Cushing Laboratory of Experimental Medicine of Western Reserve University, Cleveland.*)

This report includes (1) a brief summary of the sixth annual inventory of the state of the thyroid glands in the brook trout at the hatchery of the Blooming Grove Hunting and Fishing Club, and (2) an account of some experiments in the feeding of fresh and stale liver.

The arrangement and number of the ponds and troughs, the water supply, the strain of brook trout, and their distribution in the ponds and troughs according to age, have remained unchanged since our first observations in 1909. The crowding has gradually increased during these years, but the general external appearance of cleanliness of the ponds and troughs has not changed. Those containing the fry have always been unusually well cared for. The food, consisting of hog's liver and heart, has remained constant during the six years for all fish up to the ninth month of life, while for the past three years all fish over nine months old have been fed with hashed sea fish.

Histological examinations of the thyroids of a complete series representing specimens from all the ponds and troughs have been made yearly. The condition of the thyroid up to the time the change of food is made, *i. e.*, the ninth month of life, has not varied noticeably during these six years. All have shown marked active thyroid overgrowth, as noted in previous papers. When the food is changed to sea fish at the ninth month, the thyroid overgrowth is arrested, and the gland returns to its colloid or resting stage in about thirty-five to forty days (1). During the three years that this effect has been studied, no further hypertrophy or growth of the thyroid has been observed, although the fish remain in the ponds for a period of about two years after the change of food is instituted. On the other hand, when liver was used as the food throughout their lives in captivity, the thyroid overgrowth progressed continuously to visible external manifestations in practically all the fish by the end of the second year. The substitution of sea fish as a food has proved to be a specific curative and preventive measure under apparently the same conditions where liver as food caused continuous thyroid overgrowth.

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In previous papers (2, 3, 4) it has been suggested that the volume of water, its oxygen supply, its content of excreta (overcrowding), and the highly artificial food (liver and heart muscle) might be factors in causing the thyroid overgrowth. It was on account of the rapid regression of the thyroid overgrowth when sea fish was fed, and on account of its continuous growth when liver and heart muscle were fed, that food was more particularly suspected of playing an important part in stimulating the thyroid to this continuous growth. If this was a factor, it seemed probable that simple experiments in which the freshest liver was fed and experiments in which distinctly stale liver was fed might reveal differences in the thyroid growth. To this end the following experiments were made.

Two troughs were selected from the series of twenty-one. The fry of one were fed in the usual manner (twice daily) with the freshest liver, while the fry of the others were fed with portions of the same hashed liver as above, which had been kept in the cold chamber (11° to 15° C.) for two days. The experiments were begun on July 16 and terminated September 17, at which time the food of all fry was changed to sea fish. Two fish were taken at weekly intervals from each trough. As controls, specimens were taken from the twenty-one troughs at the beginning of the experiment, and two specimens at weekly intervals from one adjoining trough, which were fed on the general stockroom supply. At the end of the two months there were no gross changes in size, activity, or general appearance in the two sets. Histological preparations were made from all these thyroids. Study of the condition of the thyroids showed that there was a slight gradual increase in the degree of thyroid overgrowth noticeable in the second month in those fed with the freshest liver over those fed with the same liver held for two days. No difference could be distinguished between those fed with the freshest liver and the controls fed from the general supply.[1]

[1] Similar experiments have been carried out on rats, where better control could be had. Thus two series of twenty-one young rats each were divided into groups of three each. The first group was fed on the fresh hog's liver, from animals killed the same day; the second group was fed with the same amount of the same liver one day old; and each subsequent group was fed with the same liver one day older than the preceding group. It was kept at room temperature screened from flies. They were fed with liver six times weekly, while bread and water were kept continuously in the cages. All gained in weight, those getting the freshest liver slightly more than those getting the staler liver. One rat in each group was killed at intervals of two weeks, and the thyroids were examined microscopically. There was distinct hypertrophy, as judged by the reduction in stainable colloid and increase in the size of thyroid cells, in those groups getting liver 1, 2, and 3 days old, while those getting fresh liver and liver 4, 5, and 6 days old had normal or nearly normal glands.

These findings were the reverse of what I thought might occur, as I had in mind the possibility that autolysis and bacterial digestion of the liver might produce substances capable of stimulating the thyroid cells to increased activity.

A plausible explanation for these findings is not at hand. The lack of control over the amounts of liver taken by the fish seemed suggestive, but experiments with rats where the quantity was controlled show in general the same results. The idea that certain products of autolysis and bacterial decomposition of the liver act as irritants to the thyroid may be abandoned. Since controlled experiments show only a very slight thyroid hypertrophy, one may conclude that the diet is only a contributing factor, and that it may act by increasing the work of the thyroid in order to maintain a general increase in metabolism, especially in connection with the overfeeding of a nutritionally incomplete diet.

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The Frequency of Duct-Like Spaces in the Thymus Gland, with Remarks on the Formation and Fate of Hassall's Corpuscles

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THE FREQUENCY OF DUCT-LIKE SPACES IN THE THYMUS GLAND, WITH REMARKS ON THE FORMATION AND FATE OF HASSALL'S CORPUSCLES

By DAVID MARINE, M.D., from the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland, Ohio

Of the many unsettled problems in the anatomy of the thymus gland that of the formation and fate of Hassall's corpuscles would appear easiest of solution. Nevertheless there are three theories concerning their origin that have obtained the support of different groups of observers.

First. The theory of Afanassiew[1] maintained that Hassall's corpuscles arose from the blood vessels by a proliferation of their endothelium and therefore were essentially involutionary products of mesodermal origin—the results of an obliterating angitis. This view was shared by Cornil and Ranvier[2].

Second. The theory of Hammar[3] maintains that Hassall's corpuscles are of endodermal origin, and are formed by the proliferation of one or more reticulum cells during the physiologically active periods of the thymus and therefore are not involutionary products.

Third. This view also admits their endodermal origin, but that in their fully developed state they represent the involutionary hyalinized state of the original thymic tubules (ducts of Remak) and cords.

The data which I wish to report favor the third view, and are drawn from the less studied fields of pathology and congenital developmental defects instead of the more studied fields of embryology. They are tabulated as follows:

Animal	Total No. Specimens	Specimens with Hassall's Corpuscles	Specimens with Duct Remnants	Specimens with Ducts and Hassall's Corpuscles	Specimens with large Cystic Spaces	Specimen with no Hasssall's Corpuscles
Old sheep	9	9	3	3	1	0
Young sheep (lambs)	10	10	4	4	2	0
DOGS Series T	98	95	22	19	9	3
DOGS Series A	177	172	36	31	8	5
Chicks	79	79	5	5	0	0
Man	126	126	1	1	0	0

Old Sheep Thymus Glands—9 specimens—All contain well formed Hassall's corpuscles. Three have, in addition, duct remnants or partially formed Hassall's corpuscles, and in one of the three there are numerous persistent ducts and a correspondingly small number of well formed Hassall's corpuscles.

Lambs' Thymus Glands (6-7 mos.)—10 specimens—All contain well formed Hassall's corpuscles; four have, in addition, duct remnants and forming Hassall's corpuscles; and two of the four have extensive, large, irregular cystic spaces containing an albuminous debris in which are shed epithelial cells and leucocytes (mononuclears and eosinophiles).

Dog Thymus Glands (1) Series T.—98 specimens, 60 males and 38 females, taken without selection from the several laboratories and examined expressly for the thymus. Twenty-two (15 males and 7 females) have persistent thymic ducts. Nine contain extensive cystic spaces, of which three contain no formed Hassall's corpuscles. Nineteen therefore have both duct spaces and formed Hassall's corpuscles. As regards the development of

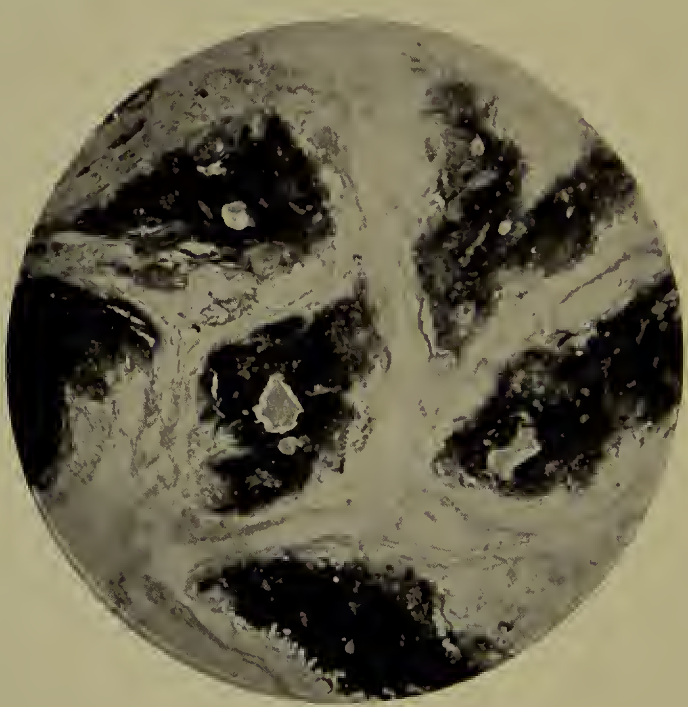

Fig. 1
Thymus of dog, showing duct-like spaces in the thymic lobules.

the thymic lymphoid tissue, two specimens contained both well developed lymphoid tissue and duct spaces, while in the remaining 20 the lymphoid tissue was either unvolutionary or had never been highly developed. While it is possible that the best de-

veloped of lymphoid tissue is favored by the normal development of the Hassall's corpuscles, with our material this is only a possibility.* (2) Series A—177 specimens taken as part of the routine post mortem examination of dogs used in other work. Thirty-six specimens have duct remnants. In 8 the cystic spaces were very extensive and the lymphoid tissue very atrophic. In 5 of the 8 with extensive cystic spaces, no evidence of formed Hassell's corpuscles was present. The number of Hassall's corpuscles is in general inversely proportional to the number and size of the ducts. Regarding the relation of the thymic lymphoid tissue development to the extent of duct persistence, the tendency, as in Series T, is for the best development of lymphoid tissue to be associated with the best development of Hassall's corpuscles.

In both Series T, and Series A, notes were made of the weights and anatomical state of the thyroids, together with the sex of the animals, but there was no evidence of any relationship between the thyroid state or sex and the presence or absence of ducts in the thymus.

Chick Thymus Glands (adults)—79 specimens—In 5 instances the slightest evidence of duct remnants were seen. All specimens contain approximately the same relative number of Hassall's corpuscles. The Hassall's corpuscles in chicks are small, and usually lack the concentric arrangement and hyalinized appearance seen in mammals, possibly because the thymus persists as an active organ.

Human Thymus Glands—126 specimens from autopsies. In but one instance—that of a girl 11 years old—was there any evidence of ducts. In this case there were both well formed Hassall's corpuscles and small duct-like remnants widely scattered throughout the gland but surrounded by well developed zones of lymphoid tissue.

Anatomy of Hassall's corpuscles—(*a*) The most common form seen in the adult thymus of man, the dog, the sheep, the ox, et cetera, is a rounded or slightly elongated island of endodermal cells, varying from 0.025—0.1 mm. in diameter, and surrounded

*Foot Note—*Parathyroids* embedded in the thymus were found accidentally in the portion taken for section in two instances. Two transverse sections of the thymus area were taken in each case, and therefore only a small portion of the thymus was examined. The thymus is a common location for accessory parathyroids.

by a delicate fibrous capsule—the remains of the limiting membrane of the embryologic tubule or cord. Within this delicate fibrous capsule are several layers of large crescentric epithelial cells concentrically placed within the capsule, and in the center of which is a mass of nuclear debris and some dense hyaline cystoplasmic or plasmic remains. The outermost cells lying just

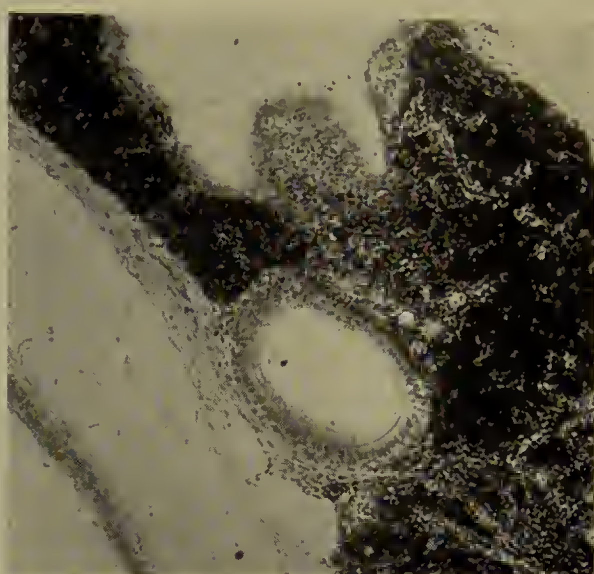

Fig. 2
Higher magnification, showing the ciliated columnal epithelium.

within the capsule usually have the best preserved nuclei and cytoplasm while the remaining layers show progressively increasing veratinization. Departures from this type are frequent. (*b*) Another common type of Hassall's corpuscles seen especially in man consists of a delicate fibrous capsule with a single layer of flattened partially degenerated cells, and the rest of the space filled with granular, cheesy, albuminoid debris, in which the outlines of swollen, degenerated, epithelial cells and leucocytes occasionally may be made out. They resemble somewhat minute sebaceous cysts. These cyst-like Hassall's corpuscles may reach 1 mm. in diameter and present the gross appearance of milary abscesses—the so-called Dubois abscesses. Chiari[4] has recently carefully studied this form and has shown that they are not broken down gummata, as Dubois believed, but represent a special type of metamorphosis in which hydration of the epithelial cells instead of desiccation take place. (*c*) Another form of Hassall's corpuscles seen especially in the very young mammal, and which is the usual form in birds, consists of nests of well preserved

polygonal epithelial cells with slight or no evidence of compression or hyalinization. (*d*) In addition to the above so-called normal forms, one sees duct-like spaces and remnants in which all stages of the transformation into true Hassall's corpuscles may be made out. Schambacher[5] has recently made a very careful study of these persistent ducts in the human thymus. They are comparatively rare in man while in dogs they are very common.

Origin of Hassall's Corpuscles—(1) The view supported by Afanassiew, Cornil and Ranvier is now of historical interest only. Attempts to inject these structures by way of the blood vessels have invariably been failures. Also, the Hassall's corpuscles are most numerous and best developed, on the average, at a much earlier period in life than the occurrence of obliterative changes in the vessels or the normal involution of the lymphoid elements. During involution of the thymus the vessels undergo obliterative changes quite similar to those seen in the involuting uterus and may come to resemble somewhat true Hassall's corpuscles.

(2) It is now generally accepted that the corpuscles arise for the original thymic anlage which is of entodermal origin from the 3rd pair of gill clefts (the thymus anlagen from the 4th gill clefts are negligible in mammals as regards the thymus as an organ). It is the prevailing opinion at present that the thymus reticulum also is derived from the endoderm, and Hammar, on the basis of his extensive studies, states that Hassall's corpuscles arise from the proliferation of single reticulum cells during the period of active development of the thymus.

(3) This is where the division of opinion occurs, since it does not explain the fate of the original thymic ducts, nor the presence after birth of the developmental abnormality of extensive duct-like remnants in 20 to 25 per cent of the thymus glands of dogs with a corresponding decrease in true Hassall's corpuscles. As the literature reports indicate and our own observations confirm, all mammals show this developmental defect to some extent. It is difficult to understand how such orderly arranged columnar and ciliated epithelial lined glandular spaces could arise from single cells already differentiated toward reticulum formation. Then, too, other observers have noted, and in my series it is most striking, that the number of well formed Hassall's corpuscles varies inversely with the number of duct remnants.

Schambacher has shown in human thymus glands that all degrees of Hassall's corpuscle formation, from true ducts to true Hassall's corpuscles, may be present in the same gland. In

Fig. 3
Projection sketch of duct-like space with colloid-like contents in which are leucocytes and desquamated epithelial cells. Surrounding lymphoid tissue slightly atrophic and thickening of the blood vessels.

dogs this is of much more frequent occurrence, so that in a large series of glands one sees instances where the duct remnants are so extensive that no formed Hassall's corpuscles are present, and in a larger group of cases still both ducts and formed Hassall's corpuscles are present, while in a third and still larger group only formed Hassall's corpuscles are present.

Lymphoid tissue is arranged about the duct-like spaces just as it is about the well-formed Hassall's corpuscles. Hence, the ducts occupy the same relative positions in the thymus that the normal Hassall's corpuscles do. It has seemed that in those cases with marked development of the ducts the lymphoid tissue was not so well developed as in the cases where the Hassall's corpuscles were well formed. The relationship of the ducts to the Hassall's corpuscles is so uniform and constant that whatever explanation suffices for one will suffice for the other.

The thymic tracts in the beginning are tubules. These primary tubules give rise, in early embryonic life, to secondary epithelial cords out of which the Hassall's corpuscles are formed when they are broken up into islands by the ingrowth of connective tissue. There is general agreement that these epithelial cords are potentially capable of differentiating into tubules just as the parent tubules may be so differentiated in the beginning.

Any explanation as to the cause of this further differentiation in some instances and its absence in others, as to the relative frequency in some animals and its relative rarity in others, must

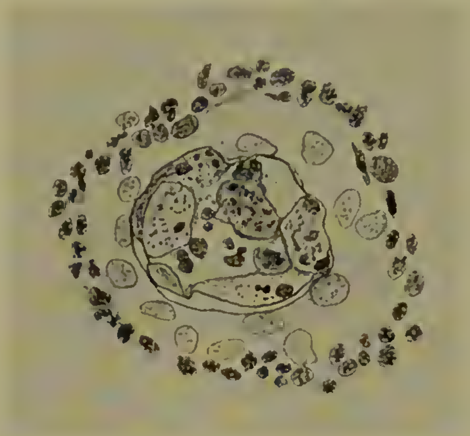

Fig 4
Projection sketch of a Hassall's corpuscle with evidence of the original duct lumen present.

take into account some physiological stimulus as the potent factor controlling the degree of anatomical differentiation. The thyroid is a notable example of this kind of control over the development and fate of its tissues. Thus the thyroglossal

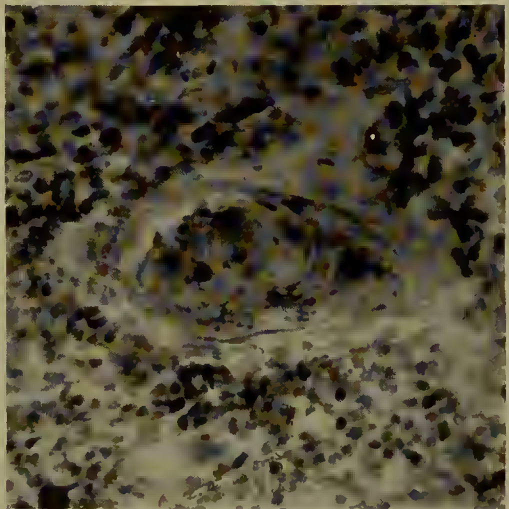

Fig. 5
Elongated Hassall's corpuscle from a dog, with core composed of the compressed contents of the pre-existing tubule.

tract normally undergoes total absorption in the second and third months of intra-uterine life, but under what appears to be the stimulus of functional necessity such absorption may be delayed or wholly prevented. In markedly goitrous districts it

may be present in 90 per cent of the cases coming to autopsy, while in non-goitrous districts such persistence does not occur. In other words, the development of permanent thyroid tissue in the thyro-glossal tract is associated with the overgrowth of the whole thyroid anlage at a time before the tract should be absorbed. It is probably some such regulatory process that determines in a given thymus whether further differentiation of the cords into tubules is to occur or whether involution is to begin before such differentiation has taken place. The nature of this stimulus is unknown, but it is suggested that it is an integral part of the mechanism controlling thymus function. According to this view, whether the Hassall's corpuscle is a tubule or a solid epithelial mass would depend largely on the degree of epithelial differentiation at the time the involution began.

One sees in mammals, especially dogs, a complete series of Hassall's corpuscles ranging from the highest differentiation into tubules lined with ciliated columnar epithelium and containing epithelial cells, leucocytes and albuminous debris, downward through smaller tubules with flattened hyalin epithelial lining and a core of compressed hyalinized cytoplasmic and nuclear debris (the remains of the tubular contents), and lastly well formed hyalinized concentric corpuscles where no trace of a previous tubular differentiation may be made out. The occurrence of this series of anatomical changes could best be explained on the theory that both the ducts and the cords arise from the same tissue and undergo a similar involution, which, in the case of the cords, results in the formation of the so-called typical Hassall's corpuscles before birth, in the case of the small ducts also results in the formation of fairly typical Hassall's corpuscles, the development of which may continue after birth, and lastly in the case of the larger ducts in the failure to reach that degree of involution even during extra-uterine life.

The formation of Hassall's corpuscles in an involutionary and regressive process. It begins early in foetal life with a shrinkage of the cells of the primary tubules and epithelial cords and their compression by the developing lymphoid tissue. Next these masses pass through a stage of hyalin transformation or keratinization (in man not infrequently a liquifaction takes place instead of desiccation, and cyst-like types of Hassall's corpuscles are formed as already mentioned). Still later, during the involution of the lymphoid tissue calcification may occur, and many

are wholly absorbed. This sequence of degenerative changes is the usual physiological process utilized by the organism generally in its attempt to eliminate inactive tissues. Regeneration of tissues thus degenerated is unknown, and while it has been stated to occur in Hassall's corpuscles in association with regeneration of the lymphoid tissue of the thymus, the evidence is quite against it. There is no well-founded experimental evidence that the thymus lymphoid cells can undergo secondary regeneration. In certain diseases in man, as acromegaly, myxodema, Basedow's syndrome, Addison's disease, myasthenia gravis, etc., following Marie's[6] view it is believed to occur. On the basis of a considerable acquaintance with Basedow's syndrome, I am inclined to this belief also in the case of this particular syndrome, and in such cases one may see very marked lymphoid hyperplasia (?) (persistence) with the Hassall's corpuscles reduced in number and very atrophic—a condition never seen during the fullest development of the organ in early life.*

Summary

Normal Hassall's corpuscles represent the atrophic and hyalinized remains of the embryologic thymic epithelial tubules and cords. The frequency of atypical development of Hassall's corpuscles varies in different species of animals. In dogs duct-like epithelial lined spaces were present in 58 of 275 cases, or about 21 per cent, while in man they were present in one of 126 autopsies. In the sheep and chick the series is too small for percentage consideration. Starting with the embryonic epithelial tubules and cords, there is a considerable range of possible morphologic changes. Thus the solid cords may differentiate into tubules before the involutionary process starts, or the involutionary process may start before tubular formation takes place. In the latter case, which even in dogs is about 80 per cent of all cases, typical Hassall's corpuscles are formed, while in the former, varying degrees of atypical Hassall's corpuscles are formed, depending on the extent of the tubular differentiation before involution begins.

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*In a recent paper, Hart[7] expresses the view that the Hassall's corpuscles are physiologically active throughout life and may even be independent organs related to the thymus in some such way as the Islands of Langerhaus are to the pancreas.

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EPITHELIOMA OF THE PHARYNGEAL MUCOSA IN A FOWL

By DAVID MARINE, M. D., from the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland, O.

The comparative incidence of tumors is deemed of sufficient importance to justify recording the following case, which came under my observation incidentally in the course of some work on goitre in fowls.

The fowl—a female white Orpington, serial No. 2372, aged nearly two years—was one of several sent to me by Doctor Chevalier Jackson, of Pittsburgh, Pa.

Upon arrival on February 5, 1915, the fowl weighed 2720 gms. Well nourished. Feathers glossy and normal. Left thyroid lobe palpable, probably the size of a pecan. Breathing through mouth with very definite dyspnoea. Odor of breath was distinctly foul. There is a slight fulness on the left side below the angle of the jaw and including the larynx, and to the touch it appears as a localized hard mass 3 or more cm. in diameter, below and free from the skin. Examination of the mouth showed a large, circular fungoid mass of a pale yellow color rising abruptly from the surrounding mucosa, which was slightly hyperaemic. On cutting into it a piece was easily broken out having a dry, firm, yellowish and necrotic appearance. The general impression gained was that of a chronic infectious granulomatous process, with extensive necrosis, compressing and displacing the larynx. Externally the skin surfaces are everywhere clean.

February 12. General condition the same. Microscopic examination of the tissue secured at the time of the first examination shows uniform dry necrosis with extensive cellular infiltration and the outlines of an irregular stroma. The free surface was covered with mucus containing both red corpuscles and leucocytes.

The fowl had considerable difficulty in swallowing, and appeared to be getting weaker.

February. 20. Killed by bleeding. Weight, 2,570 gms. Autopsied at once. Thyroids are enlarged; right lobe, weight 1.26 gms., and left lobe, 0.79 gms. Parathyroids are only slightly enlarged, about 3 mm. in diameter. Heart slightly hypertrophied. Ovaries small. Other thoracic and abdominal organs appear normal.

Mouth and Pharynx. Projecting from the left lateral wall and roof of the pharynx is a sharply circumscribed tumor-like mass measuring roughly 4 cm. in greatest anterior-posterior diameter, 3 cm. in its greatest transverse diameter, and averaging about 1cm. in thickness. The mass projects anteriorly nearly to the left angle of the mouth. The tongue is quite free, as is also the larynx, which is pushed to the right and rotated so that the glottis opens opposite the cratered, ulcerated center of the tumor. The periphery of the tumor extends under the pharyngeal mucosa, giving the appearance of the normal pharyngeal mucosa, extending a slight distance on to the tumor. It is firmly adherent to the jaw bones on the left side. Externally the subcutaneous tissues are free and normal. No metastases were made out. The general position of the tumor is shown in Fig. 1. No other lesions of the buccal or pharyngeal mucosa were made out.

FIG. 1
Photograph of head with pharynx and mouth opened on right side, showing tumor mass in the centre of the field; (a) glottis; (b) cratered ulcerated centre of the tumor; (c) normal pharyngeal mucosa extending up over the edge of the tumor.

Microscopic Examination. Sections taken through the border of the tumor show the mucosa around and extending on to the tumor to be normal. The complete necrosis of the tumor adjoining the mucosa masks the recognition of any possible transitional zone. Practically the entire thickness of the tumor is necrotic. Everywhere on the base of the tumor there is a thin, irregular zone of epithelial tissue arranged in columns and strands of cells invading the entire thickness of the muscular wall of the pharynx and projecting slightly into the loose fascial coat. More anteriorly the bone of the lower jaw is similarly infiltrated. No epithelial pearl formations or prickle cells are made out. Occasionally the invading cell columns have a slightly glandular appearance seen in the so-called basal cell types of epithelioma in man. The line of necrosis is sharply marked by a dense zone of leucocytes associated with slight extravasation of red blood cells. Only the outlines of the irregular stroma can be distinguished in the necrotic part. The general appearance of the invading columns of tumor cells is shown in the accompanying photomicrograph, Fig. 2.

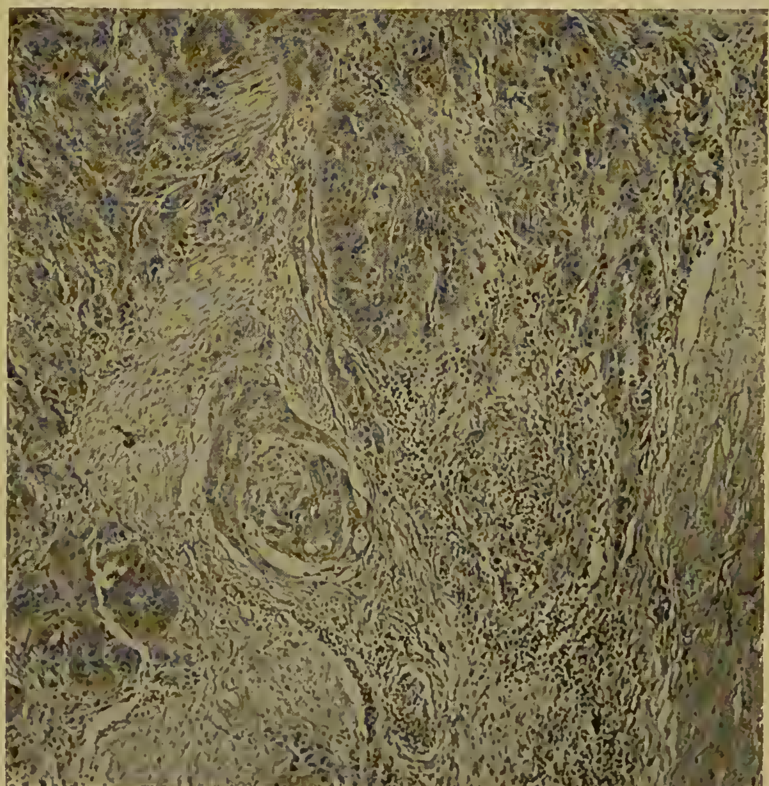

FIG. 2
Photomicrograph from base of tumor, showing type of cell growth and invasion of the muscular coat of the pharynx. X 100.

Morphologically this tumor is a carcinoma. The possibility of its being an unusual case of the so-called "epithelioma contagiosum of fowls" can be eliminated by the absence of lesions in the usual locations, by the presence of but one lesion, by the absence of the disease from the rest of a large flock, and by the fact that the epithelial changes are very characteristic and different from those of true cancer.

Tumors closely resembling this one as regards location, gross and microscopic appearance, have been reported by L. Pick (1) and Koch (2).

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A PRACTICAL DEVICE FOR USING THE SAFETY RAZOR BLADE TO CUT CELLOIDIN SECTIONS

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A PRACTICAL DEVICE FOR USING THE SAFETY RAZOR BLADE TO CUT CELLOIDIN SECTIONS *

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One of the drawbacks to the more extensive use of routine celloidin or frozen sections has been the problem of keeping microtome blades in good condition. Almost any assistant with a week's practice can block, cut and stain sections as a routine; but it is difficult to teach laboratory assistants to sharpen and care for microtome blades, and with the more extensive employment of women for such work the problem has become acute. Also, the cost of having the blades sharpened outside may be prohibitive or the work unsatisfactory, and if done by a trained assistant it is time-consuming.

To meet these conditions, several men have attempted to utilize the safety razor blade as a microtome. One of the chief troubles has been the vibration, especially with the paraffin technic, and so far as we know no satisfactory method has been devised to get around this difficulty.

For the preparation of celloidin or frozen sections from large numbers of animal experiments, we have found the following simple device highly satisfactory: As a holder we use an old Walbe blade after straightening the edge, and having it reground if badly worn. The edge is dulled except for the portion covered by the razor blade. We have tried the several types of razor blades, and on account of the length (5.7 cm.) and double edge have found the Durham Duplex the most satisfactory. A longer blade would have advantages, but it is not necessary. The blade (3, Fig. 1) is laid on the holder so that the edge of the holder extends to the beginning of the bevel on the razor blade, allowing a free border of about 2 mm. This position is maintained by two pairs of pins set into the holder and so placed that the posterior pair (4, Fig. 1) engages the curved corners of the razor blade to prevent its slipping back, and yet does not touch the cutting edge. This pair of pins also penetrates the spring steel plate which grips the blade. The second pair of pins (5, Fig. 1) is placed slightly external to and 0.5 cm. in front of the first pair. These act as guides for the razor, facilitating its insertion and preventing any lateral motion that might allow the cutting

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edge to hit the posterior pair of pins. A plate (represented by a broken outline, Fig. 1) of spring steel, tapering to a thin edge anteriorly and slightly convex to permit the ends to engage first, grips the razor blade throughout its entire length about 0.5 cm. back of its cutting edge.

This plate is tightened by a set screw (1, Fig. 1) as shown in Figure 2. A small spring (2, Fig. 1) placed posterior to

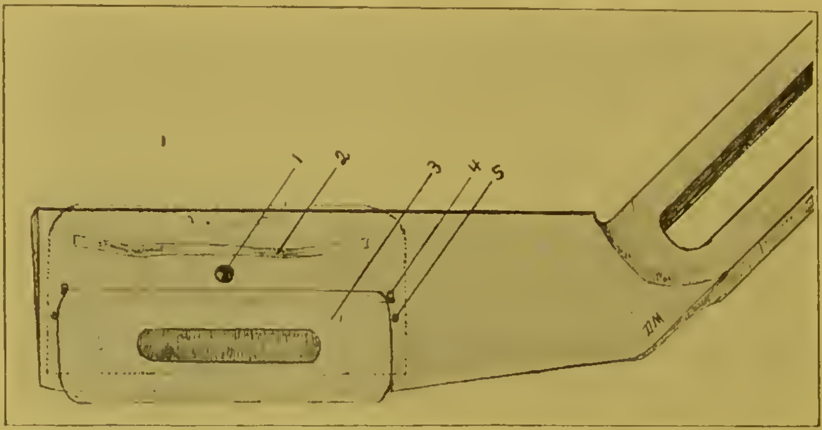

Fig. 1.—Instrument with blade holder removed. 1, Position of set screw holding the spring steel plate; 2, small steel spring to lift plate when set screw is loosened; 3, safety razor blade; 4, one of the posterior and internal pair of posts controlling position of razor blade; 5, one of the anterior and external pair of posts controlling position of razor blade.

Fig. 2.—Instrument ready for use.

the set screw, between the holder and the plate, facilitates changing or adjusting the razor blade.

This modified microtome has been in use for some months. Any one can obtain sections from 15 to 20 microns thick at a very low cost, and for the routine section work with our animal experiments it has replaced the standard microtome blades.